VOLUME 83 NUMBER 3

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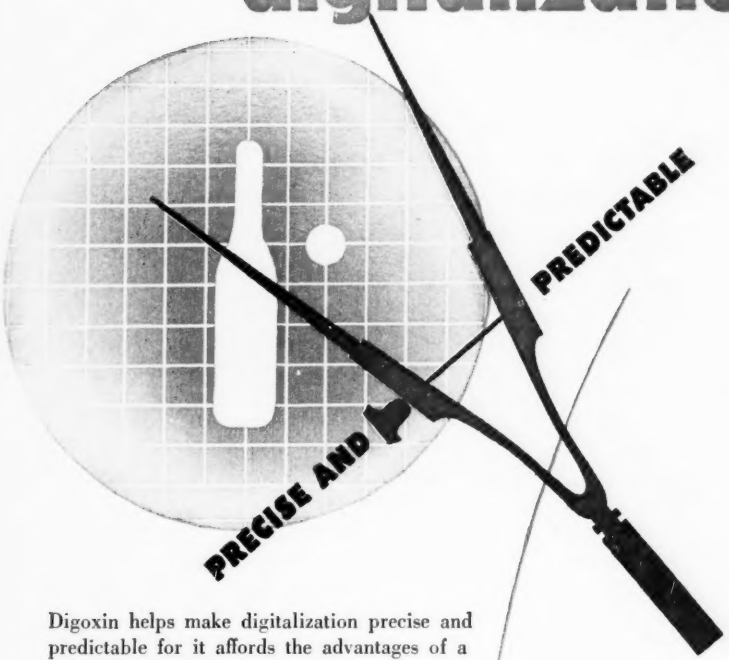
digitalization



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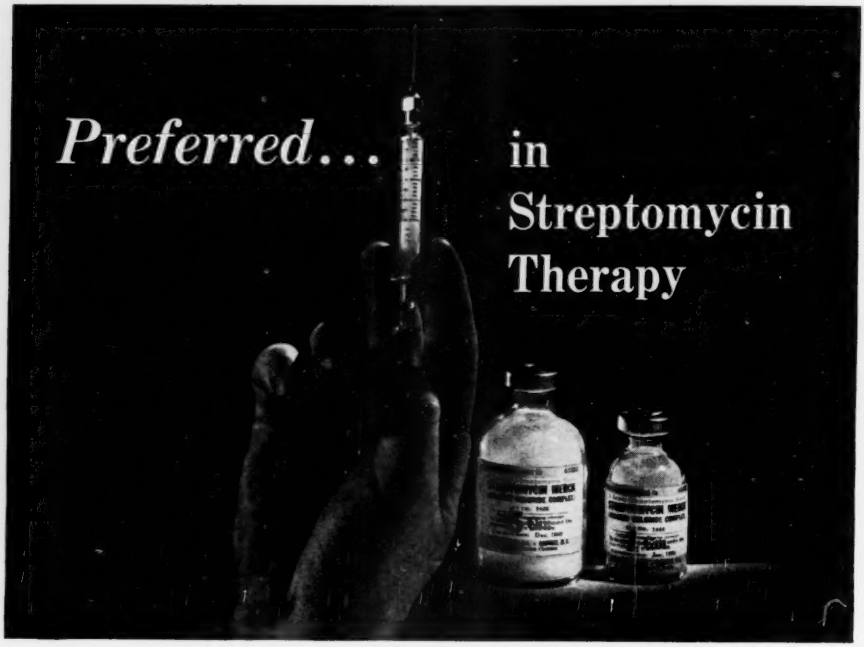

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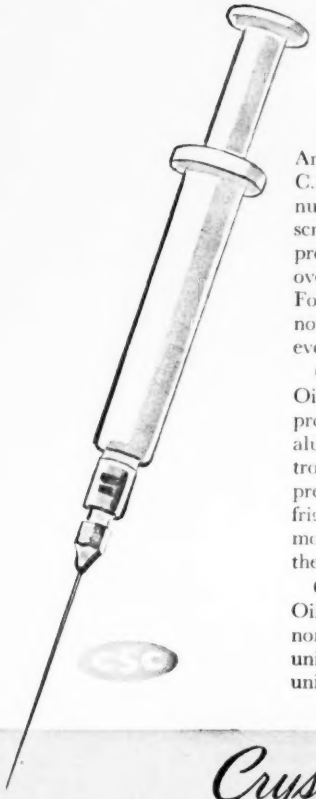

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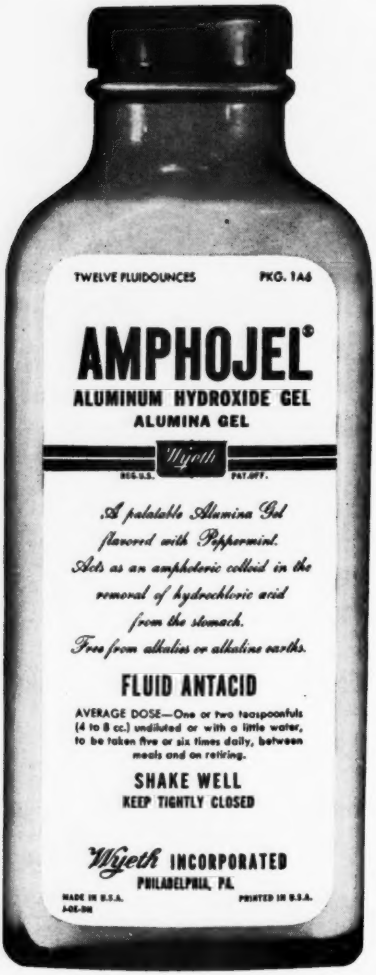

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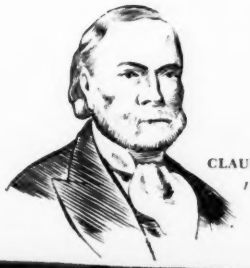

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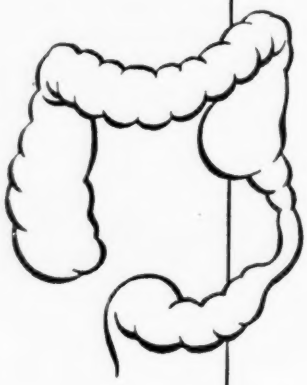

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*Collins, E. N.: The Diagnosis and Treatment of Irritable Colon: Physiologic, Local, Irritative and Psychosomatic Factors, M. Clin. North America 32:398 (March) 1948.

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MANAGEMENT OF LOWER NEPHRON NEPHROSIS

Report of Six Cases

WILLIAM S. HOFFMAN, Ph.D., M.D.
AND
DANIEL MARSHALL, M.D.
CHICAGO

THE ENTITY of lower nephron nephrosis is now well established, even though the name, coined by Lucké,[1] is a new one. It is a syndrome of severe oliguria or anuria following an initial shocklike picture and producing renal insufficiency, which in a large proportion of cases progresses to death in uremia. In many, but not all, cases an additional causative factor is trauma to muscles or red blood cells which allows hemoglobin or myoglobin or their derivatives to circulate in the plasma and be excreted in the urine. Since these compounds are less soluble in acid than in neutral or alkaline solutions, they tend to precipitate as casts in the lower nephron where concentration and acidification take place and may block the tubular lumens in this region or damage the tubular cells.[2] The kidneys in these cases are edematous, the cortex being pale and swollen in contrast with the darker than normal medulla. Microscopically, the principal lesion is confined to the lower cortex and boundary zone and consists chiefly of degeneration and necrosis of the cells of the ascending loop of Henle and distal convoluted tubules, along with interstitial edema and infiltration of cells.[3] This pathologic picture has been seen oftenest after crushing injuries to muscles, after transfusions with incompatible blood and after some intoxications with sulfonamide

From the Hektoen Institute for Medical Research of Cook County Hospital.

This study was supported by a grant from the Dr. Jerome D. Solomon Memorial Research Foundation.

1. Lucké, B.: Lower Nephron Nephrosis (Renal Lesions of Crush Syndrome of Burns, Transfusions, and Other Conditions Affecting Lower Segments of Nephrons), Mil. Surgeon **99**:371, 1946.

2. Bywaters, E. G. L., and Stead, J. K.: Production of Renal Failure Following Injection of Solutions Containing Myohaemoglobin, Quart. J. Exper. Physiol. **33**:53, 1944. Corcoran, A. C., and Page, I. H.: Genesis of Crush Syndrome, J. Lab. & Clin. Med. **30**:351, 1945.

3. Mallory, T. B.: Hemoglobinuris Nephrosis in Traumatic Shock, Am. J. Clin. Path. **17**:427, 1947. Lucké.[1]

drugs, but it also has been described after other types of severe insults to the body, such as operative shock, hemorrhage, hemoglobinuric fever, chemical and thermal burns, uteroplacental damage, alkalosis and high altitude anoxemia.

The management of lower nephron nephrosis has been varied and controversial. If the case is in the hands of a urologist, operative intervention has been almost inevitable. Ureteropelvic lavage, especially when the patient has had sulfonamide medication, is a routine preliminary step. In true cases of lower nephron nephrosis, this manipulation has had no beneficial effect. Usually after anuria or oliguria has persisted for about a week, the urologist advocates decapsulation of the kidneys, a procedure which has been tried since 1904 for almost every variety of oliguria.[4] In recent years, the decapsulation operation received strong support from Peters[5] and from Abeshouse,[6] both of whom proposed a physiologic basis for the operation and offered statistical proof of its efficacy. Peters was of the opinion that the chief factor responsible for the prolonged oliguria is the increased intrarenal pressure, which he claimed can be relieved by decapsulation. Abeshouse, on the other hand, stated his belief that decapsulation cuts the sympathetic constrictor nerve fibers to the kidney and thus increases blood floow.

However, as Thorn,[7] recently pointed out, the evaluation of the decapsulation procedure has been erroneous because of failure to recognize the natural clinical course of lower nephron nephrosis. Most of the deaths from this disease, if not due to the original insult that produced the shocklike state, occur from uremia in seven to ten days.[8] On the other hand, in those patients who have survived with conservative management (as for example the 5 patients reported on here) diuresis has been noted to begin on the fifth to the thirteenth day. If, as Abeshouse suggested, patients with oliguria should be given the test of medical management for one week and then subjected to decapsulation, the spontaneous diuresis that might occur soon after the operation would be accredited to that procedure.

Thus, the value of decapsulation cannot be gaged by the number of successful results. It is the number of failures that indicates its true

---

4. Edebohls, G. M.: Surgical Treatment of Bright's Disease, New York, F. F. Lisiecki, 1904.

5. Peters, J. T.: Oliguria and Anuria Due to Increased Intrarenal Pressure, Ann. Int. Med. **23**:221, 1945.

6. Abeshouse, B. S.: Renal Decapsulation: A Review of the Literature and a Report of Ten Cases, J. Urol. **53**:27, 1945.

7. Thorn, G. W.: Treatment of Renal Insufficiency, J. Urol. **59**:119, 1948.

8. Burwell, E. L.; Kinney, T. D., and Finch, C. A.: Renal Damage Following Intravenous Hemolysis, New England J. Med. **237**:657, 1947. Lucké.[1]

worth. Talbott,[9] for example, reported a case of unilateral decapsulation in which bilateral ureteral catheterization demonstrated equal flow of urine from both the treated and the untreated kidney. Again, in a recent case of oliguria following transfusion with incompatible blood seen by us, decapsulation was performed on the third day of oliguria. There was no immediate diuresis, but on the tenth day, after careful medical management, the output of urine became significantly large. Eventually, the patient recovered. Even though the urologist was willing to admit that decapsulation in this case was probably of no benefit, he might have been of another opinion if he had performed the operation on the eighth or ninth day of oliguria.

On consideration of the pathogenesis of lower nephron nephrosis and of the evidence available on the nature of the disturbed physiologic processes in these damaged kidneys, it appears reasonably certain that once the renal lesion has been fully developed there is no known method for producing diuresis until some degree of healing occurs. Careful biochemical observations along with specific renal function tests have been made by us[10] during both the stage of oliguria and the subsequent period of diuresis. These have led us to believe, along with others, that the persistent oliguria is produced partly by a diminished renal blood flow (and glomerular filtration rate)but chiefly by functional damage to the cells of the ascending loop of Henle and distal convoluted tubule which allows the modified glomerular filtrate nonspecifically to be resorbed with all its excretory constituents back into the tubular blood. When diuresis begins, the initial improvement appears to be due to an increase in renal blood flow and the slower recovery to improved function or regeneration of the tubular cells. Though the retained toxic products are removed within two or three weeks after the beginning of diuresis, full restitution to normal of the specific renal function takes several months.

The primary principles of our management of these cases follow:

1. After the initial shock has been controlled, the aim of treatment should not be to try to get the damaged kidney to secrete against all odds (as for example by injection of sodium sulfate,[11] by renal lavage or by decapsulation), but instead to keep the patient alive until the tubules recover sufficiently to reverse the retention of excretion products. Two diametrically opposite phenomena tend to occur simultaneously about the eighth to the tenth day; namely, functional improvement of the

9. Talbott, J. H.: Heterogeneous Renal Disorders, New England J. Med. **226**:228, 1942.

10. Marshall, D., and Hoffman, W. S.: The Nature of the Altered Renal Function in Lower Nephron Nephrosis, to be published.

11. Olson, W. H., and Necheles, H.: Studies on Anuria, Surg., Gynec. & Obst. **84**:283, 1947.

kidneys on the one hand and death from uremia on the other. The treatment should be designed to separate these phenomena by hastening, if possible, the recovery of the kidneys and by postponing the ravages of uremia with its cardiac and pulmonary complications.

2. Both aims can be favored by restoration and maintenance of an optimal nutritional state. This involves an adequate caloric and protein intake, amelioration of anemia by blood transfusions and provision of the required water-soluble vitamins.

3. The electrolyte and hyrdogen ion concentration of the plasma and extracellular fluids should be brought to as nearly normal a level as possible to maintain the integrity of the milieu in which cells normally thrive.

4. The toxicity of the retention products should be combated by both symptomatic treatment and administration of known chemical aids.

5. The retention of toxic products should be delayed as much as possible. It is for this purpose that the use of the artificial kidney,[12] peritoneal infusion[13] and intestinal lavage[14] have been advocated. If these procedures can be made safe and practicable enough to involve less risk than that involved in waiting for spontaneous diuresis, they may come into more general use. For maximal benefit they should be utilized at the time of severe nitrogenous retention, and they require adequate hospital personnel and frequent serum analyses for chloride, sodium and bicarbonate concentrations. We have had no personal experience with these methods of vicarious excretion.

Our own procedure for retarding the accumulation of toxic excretory substances has been the careful induction of edema as a method of dilution of the toxic products. If 7 to 14 liters of edema fluid of normal electrolyte composition can be retained in the period of seven to ten days, the extracellular fluid will have one and one-half to two times its original volume and the concentration of the retention products will be correspondingly decreased. Similarly, the total amount of alkali reserve will be increased. If no risk were involved in this induction of edema, its advantages would be obvious. We were aware of the potential danger to the heart and lungs in the development of edema in our cases, but we felt that this danger could be minimized by proper precautions and that

12. Kolff, W. J., and Van Noordwijk, J.: The Artificial Kidney, Kampen, Holland, J. H. Kok N. V., 1946.

13. Fine, J.: Frank, H. A., and Seligman, A. M.: The Treatment of Acute Renal Failure by Peritoneal Irrigation, Ann. Surg. **124**:857, 1946.

14. Vermooten, V., and Hare, D. M.: The Use of Continuous Gastric Lavage in the Treatment of Uremia Associated with Prostatism, J. Urol. **59**:907, 1948.

in any circumstances a calculated risk was permissible in the treatment of a disease stated to have a mortality of 80 to 90 per cent.[3]

It should be pointed out that the induction of edema does not mean "flooding the body" with fluids in the hope of forcing a passage of urine. Actually, edema occurs in these patients in any circumstances, if food and fluids are given either orally or intravenously in an attempt to maintain the caloric and protein needs of the body. This retained fluid is low in chloride and sodium, a phenomenon probably due to the loss of renal regulation of excretion of electrolytes in relation to water, Normally, the kidneys secrete urine that is hypotonic in regard to sodium and chloride, thus compensating for the relative excess of dietary fluid over dietary salt intake. When renal shutdown occurs and food intake continues, edema with hypochloremia and hyponatremia results (see case reports). Our management involves a slow increase in the quantity of retained extracellular fluid and an attempt to get its electrolyte concentration as nearly normal as possible. Experimental confirmation of the validity of this procedure is found in the work of Barry, Shafton and Ivy,[15] who demonstrated that bilaterally nephrectomized dogs lived longer when given saline solutions.

In practice the treatment consisted of intravenous injection of 2 to 3 liters of isotonic sodium chloride solution U.S.P. and 1 liter of sixth-molar sodium lactate solution during the first twenty-four to thirty-six hours after oliguria had been recognized. This preliminary treatment usually served to rule out oliguria and azotemia on the basis of dehydration and hypochloremia, for in such uncomplicated cases diuresis usually began promptly. Glucose was given for the most part in the sodium chloride solution. With the persistence of the oliguria, the recommendations on the second and third day were based on the chemical and clinical findings. Blood was given in large quantities for anemia, preferably in these first days before the nitrogenous retention and elevation in blood pressure became great. If acidosis was still pronounced, sodium bicarbonate was injected intravenously along with the other fluids.

Food by mouth was encouraged, usually in the form of a full soft diet. Vitamin B complex and vitamin C were given by mouth if possible, otherwise parenterally. Calcium gluconate injections, 20 to 40 cc. of the 10 per cent solution daily, were often an important adjuvant to combat any tendency to tetany from the low serum calcium concentrations which might become manifest when the acidosis was relieved. Calcium injections also helped to combat phosphate and guanidine retentions.

15. Barry, F. S.; Shafton, A. L., and Ivy, A. C.: Experimental Edema in Nephrectomized Dogs: Rôle of Water and Chlorides, Arch. Int. Med. **51**:200 (Feb.) 1933.

On succeeding days, the fluid prescription was usually for 2 liters of sodium chloride solution in 5 per cent glucose solution and 600 cc. of sixth-molar sodium lactate solution. Often it was for much less, if the serum chemical analyses or pulse rate, blood pressure and pulmonary findings warranted a reduction. If the edema fluid was accumulating rapidly and the concentrations of chloride and sodium were still low, 500 cc. of 2 per cent sodium chloride solution was administered slowly. Usually the patient was seen to be clinically improved after this procedure. On the days when the patient ate well without vomiting, all parenteral administration of fluids could be dispensed with and the required quantity of salt given by salt shaker with the food. If anemia was still significant, several more transfusions were given unless cardiac impairment was too great. When the patient was unable to take food by mouth, 30 to 50 Gm. of amino acids was administered intravenously. Penicillin was used prophylactically throughout the whole period of oliguria in doses of 20,000 units every three hours.

As soon as the urinary output reached 500 cc. per day, all administration of sodium chloride by mouth and vein was stopped, and the patient was treated as though he had cardiac edema. This procedure, however, was not adopted in the 1 fatal case of the 6 reported here. In retrospect, we believe that our management in this case was faulty in that we persisted in giving fluids for too long a period. Death occurred on the tenth day with symptoms and findings of severe uremia; but enlargement of the heart, hydrothorax, edema of the lungs and bronchopneumonia were also present. Though the latter conditions are common in the terminal stages of uremia even when no excess fluids are given, we felt that it might have been safer to stop intravenous administration of fluids as soon as diuresis set in. Possibly, thoracentesis would have helped. In the remaining 5 cases, careful observation of the heart and lungs, with judicious use of digitalis and aminophylline, if necessary, and the attempt to confine the fluid accumulation to the dependent portions of the body by placing the bed in Fowler's position and urging the patient to sit with his feet dangling over the edge of the bed for a portion of the day helped to prevent any dangerous sequelae to the development of edema.

This program differs from that suggested by Thorn[7] in the important detail of the quantity of fluids. Thorn advised limitation of fluids and categorically stated that many deaths may be needlessly caused by giving too much fluid. He, however, did not document this statement with cases of his own but reported 2 cases of other investigators. In 1 of these, a low serum chloride concentration developed, requiring administration of 35 Gm. of salt (presumably 4 liters of isotonic sodium chloride solution) which promptly stopped the rise in blood urea concentration. This observation is in support of our management. Our data (tables 1 to 6

and fig. 2) show that the curve of the blood nonprotein nitrogen concentration tended to level off as the edema accumulated, in spite of continuous protein intake and the persistence of severe oliguria. This leveling was due either to dilution or possibly to a diminution in protein breakdown. Kugel[16] also recommended limitation of fluid intake, but in his 2 reported cases this limitation was not resorted to in the first days of treatment. Kugel spoke of the retention of water from cellular breakdown. Actually, if this accumulation does occur, administration of saline will be required to bring its chloride and sodium concentration up to normal.

REPORT OF CASES

The following 6 histories are of patients in whom the principles discussed previously were utilized. The detailed management of each patient differed from that of the others partly as an expression of the accumulated experience from the previous cases and partly because of the necessity to compromise with the opinions held by others interested in the patient. In each of them, however, edema was slowly and carefully induced and an effort made to raise the serum sodium and chloride levels toward normal. Four patients recovered completely; 1 died in uremia and heart failure five days after diuresis had set in; the sixth patient still had some renal insufficiency four months after diuresis had first developed.

CASE 1.—M. K.,[17] a 34 year old white woman who had been in excellent health, had avulsion of almost her entire scalp when her hair was caught in the wheels of an electric sewing machine at her work. She was brought to the hospital bleeding and in shock. She responded well to injections of blood and plasma and two weeks later was considered well enough for autogenous skin graft. Toward the end of the operation, which was performed under anesthesia induced by thiopental sodium[R] (pentothal sodium), the patient went again into shock, her blood pressure dropping almost to 0. Plasma and saline solution were administered, but shock persisted. A transfusion of whole blood was given. Two hours later a temperature of 106 F. developed. At this time her blood pressure was 100 mm. systolic and 42 diastolic. She was apathetic. During the next thirty-six hours only 60 cc. of urine was passed. On the third morning the patient was stuporous; her face was bloated; the blood nonprotein nitrogen concentration was 67 mg. per hundred cubic centimeters. By the fifth day of oliguria, the nonprotein nitrogen level was 113 mg. per hundred cubic centimeters; the red blood cell count had fallen to 1,200,000 per cubic millimeter. The patient's condition was considered poor. Two liters of blood and 500 cc. of plasma, in addition to other fluids, during the next forty-eight hours produced some improvement, but the patient's condition remained grave. Dyspnea was pronounced, but roentgeno-

16. Kugel, V. H.: Management of Acute Toxic Nephrosis, Am. J. Med. **3**:188, 1947.

17. This patient was under the care of Dr. Maxwell M. Corbett and was treated in consultation with him at the Walther Memorial Hospital, Chicago. The case is reported with his permission.

graphic examination revealed no significant abnormality in the chest. Since the patient showed no tendency to vomit, she was encouraged to take food and fluids by mouth. After the eighth day, no fluids had to be given intravenously. A slight increase in urinary output occurred after the seventh day. On the tenth day, 545 cc. was excreted. Thereafter, diuresis increased rapidly so that on the fifteenth day 4,710 cc. was excreted. By this time the nonprotein nitrogen level had fallen considerably. On the seventeenth day the patient was considered out of danger.

The fluid intake consisted of 2,000 cc. of lactated Ringer's solution U.S.P. and 1,000 cc. of 10 per cent glucose solution on each of the third and fourth days, along with several ampules of sodium bicarbonate (3.75 Gm. per ampule). During the fifth and sixth days, 2,000 cc. of blood and 1,500 cc. of plasma were injected, in addition to 2,000 cc. of glucose solution and 1,000 cc. of 5 per cent amino acids in glucose solution. On the seventh day 1,000 cc. of lactated Ringer's solution and 1,000 cc. of amino acids in glucose solution were administered. On the eighth day, only 1,000 cc. of glucose solution and 1,000 cc. of amino acid solution were given intravenously. On both the ninth and the tenth day, 9 Gm. of salt was given by salt shaker, but thereafter salt was forbidden until edema had disappeared.

Table 1 shows the significant results of chemical studies on the blood and urine during the course of the illness. On the twenty-seventh day, the urine showed no abnormality; all blood constituents had returned to normal concentration and the urea clearance was 102 per cent of normal. An examination six months later failed to reveal any evidence of the previous renal illness.

Case 2.—M. B., a 49 year old Negro man who had had symptoms of duodenal ulcer for fifteen years and of partial pyloric obstruction for the last seven months, was referred to the surgical department for treatment. Vagotomy and gastrojejunostomy were performed. Immediately after the operation, a blood transfusion was begun. After 50 to 100 cc. of blood was infused, it was recognized that the wrong type of blood had been given. The transfusion was stopped and 300 cc. of sixth-molar sodium lactate solution administered. Seven hours later the patient was in shock with a blood pressure reading of 70 mm. systolic and approximately 0 diastolic. He remained in this condition for about ten hours. Oliguria set in, the patient passing less than 300 cc. of urine in the forty-eight hours following transfusion. The urine had a specific gravity of 1.006 and showed the presence of albumin and red and white blood cells. It contained pigmented casts as well. These were also present in later specimens.

The fluid management in this case was complicated by the fact that the patient had just had a serious operation and was bleeding from the stomach. Suction by means of an indwelling Levin tube removed more than 3,000 cc. of fluid daily for several days, a considerable portion of which was blood. During the first two days fluids were given in large quantities in the belief and hope that the oliguria was due to dehydration and loss of electrolytes. The intravenous injections for the sixty hours included 1 liter of blood, 500 cc. of plasma, 4 liters of isotonic sodium chloride solution, 1 liter of sixth-molar sodium lactate solution and 4 liters of glucose solution. Toward the end of the third day, injection of isotonic sodium sulfate solution was suggested on the basis of the successful results of Olson and Necheles[11] in experimental oliguria. A total of 3,400 cc. of the sodium sulfate solution was injected during the next twenty-four hours, in addition to some more blood to combat the continued bleeding. There was no recognizable immediate response to the sodium sulfate injection. On the fifth day, however, 545 cc. of urine was excreted and the output increased daily thereafter.

TABLE 1.—*Chemical Findings in Serum and Urine and Blood Pressure Changes in Case 1 (M. K.)*

Days After Onset of Oliguria	Nonprotein Nitrogen, Mg./100Cc.	Creatinine, Mg./100Cc.	Sodium, Meq./L.	Chloride, Meq./L.	Carbon Dioxide, Cc./100Cc.	Total Protein, Gm./100Cc.	Hemoglobin, Gm./100Cc.	Urinary Volume, Cc./24 Hr.	Urinary Nonprotein Nitrogen, Gm./24 Hr.	Blood Pressure, Mm. Hg.
2	37.5	2.0	.....	.....	....	....	....	125	....	90/30
3	67	....	140	84	50	4.3	8.5	50	....	100/42
5	113	10 2	136	78.5	45	5.2	3.3	95	....	124/50
7	124	....	132	85	54	4.7	8.1	234	....	.....
10	145	11.2	133	88	....	....	12.2	545	2.7	170/100
14	100	....	143	98	51	6.0	11.5	4310	....	.....
16	.....	....	.....	.....	....	....	....	4453	16.9	.....
27	27.5	....	144	107.5	53	7.0	11.5	.....	....	130/90

On the ninth day the patient excreted 1,900 cc., which contained 10.35 Gm. of nonprotein nitrogen. Because of the continued bleeding and the progressive development of uremia, anemia had become severe. For that reason, 500 cc. of blood was given on each of the four days, as well as 2,000 cc. of isotonic sodium chloride solution. But the serum chloride concentration, which had fallen to 80 milliequivalents per liter, was little improved by the injections. The patient's edema became severer. Penicillin injections, 20,000 units every three hours, had been kept up during the entire postoperative period.

In spite of the satisfactory urinary excretion and the well established edema, the serum nonprotein nitrogen concentration rose from 176 mg. per hundred cubic centimeters on the fifth day to 243 mg. on the ninth day. The blood pressure on the ninth day was 180 mm. systolic and 118 diastolic. The serum potassium level rose to 39.5 mg. per hundred cubic centimeters, a concentration which may have been an important contributing factor to the myocardial damage. The rapid rise in the serum nonprotein nitrogen and potassium levels indicated an accelerated breakdown of tissue of a degree not seen in the other cases. On the ninth day, uremic symptoms were quite evident, as were those of heart failure. In spite of emergency cardiac management, which unfortunately did not include thoracentesis, the patient died on the tenth day.

The following principal pathologic observations, in addition to those of duodenal ulcer and gastrojejunostomy, were revealed on autopsy: lower nephron nephrosis, with renal edema and focal glomerulitis, hypertrophy and dilatation of the heart, ascites, bilateral hydrothorax, coronary sclerosis, central necrosis of the liver, hemorrhagic erosion of the stomach, enteritis and hemorrhages into the pelves of the kidney and into the urinary bladder.

The microscopic description of the kidney was as follows:[18]

The glomeruli were for the most part normal except for moderate thickening of the basement membrane and the presence of polymorphonuclear leukocytes in some loops. Occasionally, hyalinized glomeruli were seen. The cells of the proximal convoluted tubles were somewhat swollen and hazily outlined. The lumens were frequently dilated and contained eosinophilic granular precipitate.

In the lower nephrons, especially in the distal convoluted tubules, brown or copper-colored casts were seen. These were granular or smooth; occasionally, they looked like frayed ribbons or formed spherules similar to erythrocytes. The tubules of the lower segment showed serious damage, especially in the areas where the heme casts were present. Circumscribed or diffuse dilatation of the lumens of some tubules could be observed. The epithelial cells showed all variations between degenerative and necrotic changes, in some areas complete disintegration. In many tubules of the lower nephrons there were signs of regeneration characterized by flattened cells with basophilic cytoplasm and dark-staining nuclei. The interstitial capillaries were congested. Occasional deposition of calcified material in tubules was observed. Some of the arteries showed intimal proliferation.

A section of the kidney showing the casts and changes in the distal convoluted tubules is shown in figure 1. Table 2 shows the results of chemical studies in the blood and urine during the course of the illness.

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18. Dr. Paul B. Szanto, of the department of pathology of Cook County Hospital, Chicago, reported the observations at autopsy and prepared and described the microscopic sections.

CASE 3.—A. V., a 23 year old Negro woman, had had chills and fever for five days with repeated spells of vomiting. She was admitted to the hospital in collapse with a blood pressure reading which was 90 mm. systolic and indeterminable diastolic. No history of the use of sulfonamide drugs could be obtained. Clinical and roentgenographic examination revealed the presence of right lobar pneumonia. The immediate treatment consisted of injections of penicillin and intravenous administration of 1,000 cc. of glucose in isotonic sodium chloride solution and 1,000 cc. of 10 per cent glucose solution. On the third morning it was recognized that the patient had not urinated since the specimen obtained by catheterization on her admission. A second catheterization now produced 200 cc. of straw-colored urine of specific gravity 1.011, with protein, red and white blood cells and granular casts. During the next forty-eight hours the patient received 2,000 cc. of isotonic sodium chloride solution and 2,000 cc. of 5 per cent glucose solution, in addition to 24 Gm. of sodium bicarbonate orally. But the oliguria

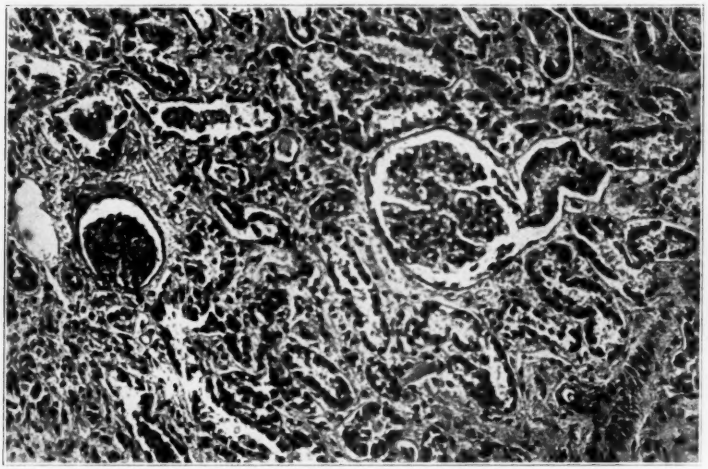

Fig. 1.—Section of kidney showing granular casts in distal convoluted tubules. The lining epithelium of these tubules is flattened. The interstitial tissue is edematous and infiltrated with round cells.

persisted, the blood nonprotein nitrogen concentration rose rapidly, reaching 185 mg. per hundred cubic centimeters by the seventh day. During the intervening days, administration of fluid was haphazard, the diagnosis of lower nephron nephrosis having not yet been fully established. On the seventh day, the patient showed some edema, but her serum chloride concentration was 87 milliequivalents and serum sodium concentration 132 milliequivalents per liter. Uremic frost was noticeable, as were other symptoms of uremia. On each of the seventh and eighth days 3,000 cc. of isotonic sodium chloride solution and 900 cc. of sixth-molar sodium lactate were administered. Glucose was given in these saline solutions. On the ninth day, only 500 cc. of isotonic sodium chloride solution and 300 cc. of sixth-molar lactate solution were administered. A pericardial friction rub was

TABLE 2.—*Chemical Findings in Serum and Urine and Blood Pressure Changes in Case 2 (M. B.)*

Days After Onset of Oliguria	Non-protein Nitrogen, Mg./100 Cc.	Creatinine, Mg./100 Cc.	Sodium, Meq./L.	Chloride, Meq./L.	Carbon Dioxide, Cc./100 Cc.	Potassium, Mg./100 Cc.	Calcium, Mg./100 Cc.	Inorganic Phosphorus, Mg./100 Cc.	Total Protein, Gm./100 Cc.	Indican	Urinary Volume, Cc./24 Hr.	Urinary Non-protein Nitrogen, Gm./24 Hr.	Blood Pressure, Mm. Hg.
3	96	6.7	133	90	44	29.8	9.4	4.1	5.4	++	100	.....	140/90
4	135	8.3	134	93.7	35	29.0	.....	.....	5.8	+++	.....	.....	130/90
5	176	9.1	139	82	44	29.8	6.9	2.7	6.1	++++	545	.....	142/90
6	188	11.4	145	82.5	46	21.2	9.5	4.5	6.5	++++	1000	.....	160/100
7	215	12.0	145	87.5	44	21.5	7.1	6.4	6.5	++++	1330	6.1	164/108
8	224	12.2	147	90	44	.....	7.7	8.2	7.0	++++	1800	7.5	180/118
9	243	12.4	148	.....	49	39.5	7.1	16.6	6.6	++++	1900	10.4	180/118

audible. On the tenth day, the urinary output was 550 cc. Now all intravenous administration of fluids was stopped and a regimen low in salt instituted. Diuresis increased steadily until 3,350 cc. was excreted daily. This high output was maintained for nine days. By this time the edema had disappeared and the serum chloride and sodium concentrations had returned to normal (see table 3). The serum nonprotein nittrogen level fell to 80 mg. per hundred cubic centimeters by the eighteenth day but was not completely normal until the thirty-first day. Figure 2 shows the relation of urinary output to results of serum chemical studies. It will be noticed that the ratio of the urinary nonprotein nitrogen concentration to that of serum rose only slowly during the first days of diuresis, becoming much greater as renal function improved. Specific renal function tests performed serially during the recovery period demonstrated that severe dysfunction of the

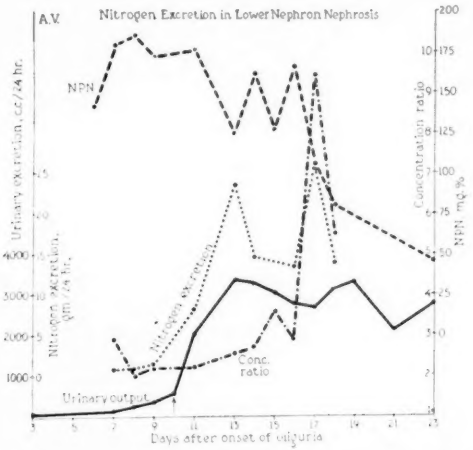

Fig. 2.—Curves showing changes in serum nonprotein nitrogen concentration in case 3 (A.V.) in relation to urinary output of water and nonprotein nitrogen and to the concentration ratio. The latter is the ratio of the concentration of nonprotein nitrogen in the twenty-four hour sample of urine to the nonprotein nitrogen concentration in the serum.

tubular cells of the lower nephron was still present even as late as at two months. However, at six months renal recovery was shown to be complete.

Case 4.—H. K., a 45 year old white woman, was admitted to the hospital in labor. Her history and physical findings showed nothing abnormal. The baby was delivered spontaneously and normally, but during expulsion of placenta approximately 700 cc. of blood was lost. The patient went into shock, her blood pressure falling to 58 mm. systolic and approximately 0 diastolic. The bleeding from the uterus continued in spite of packing. Blood and plasma transfusions were given, but the patient remained in shock for at least six hours. Forty hours later it was recognized that the patient had not urinated since the time of delivery. Catheterization yielded 45 cc. of dark-colored urine of specific gravity 1.017 with a trace of albumin and some red and white blood cells and pigmented

TABLE 3.—*Chemical Findings in Serum and Urine and Blood Pressure Changes in Case 3 (A.V.)*

Days After Onset of Oliguria	Non-protein Nitrogen, Mg./100 Cc.	Creatinine, Mg./100 Cc.	Sodium, Meq./L.	Chloride, Meq./L.	Carbon Dioxide, Cc./100 Cc.	Potassium, Mg./100 Cc.	Calcium, Mg./100 Cc.	Inorganic Phosphorus, Mg./100 Cc.	Phenol, Mg./100 Cc.	Albumin to Globulin Ratio, Gm./100 Cc.	Urinary Volume, Cc./24 Hr.	Urinary Non-protein Nitrogen, Gm. 24 Hr.	Ratio of Urinary to Serum Non-protein Nitrogen	Blood Pressure, Mm. Hg.
3	104	8.0	.....	....	....	....	....	....	....	.....	55	...	....	90/82
6	142	9.4	130	85.5	40	....	....	....	....	.....	100	0.71	2.9	110/60
8	185	10.2	134	91.3	37	21.8	....	....	2.7	2.2/3.7	240	1.3	2.2	142/74
10	182	10.1	134	100	41	21.0	7.5	13.0	....	2.7/3.3	550	....	....	148/94
11	176	10.0	137	100	42	20.7	9.2	13.4	....	2.9/3.3	2050	8.2	2.3	140/92
13	170	8.7	139	103	48	20.2	9.7	10.8	....	3.4/4.4	3350	23.4	4.1	130/88
16	125	5.6	.....	104	44	19.0	....	....	....	3.0/3.4	2750	13.3	3.9	124/90
18	80	4.8	.....	102	....	...	....	....	1.5	3.9/4.4	3150	13.9	5.4	.....
24	41	2.2	140	108	39	18.0	....	....	1.3	4.4/3.8	3350	10.1	7.3	.....
31	20	1.4	147	106	52	19.0	10.2	7.5	....	4.3/3.9	3300	7.9	12.0	120/80

casts. By the third day, the persistent oliguria was associated with a serum nonprotein nitrogen concentration of 104 mg. per hundred cubic centimeters. Edema was present.

Five hundred cubic centimeters of blood was given on each of the third, fourth, fifth and seventh days. On the third day 3,200 cc. of fluid was administered in addition to the blood, of which 1,500 cc. was isotonic sodium chloride solution and 600 cc. sixth-molar sodium lactate. On the fourth and fifth days approximately 1 liter of saline-lactate solution was given daily, in addition to 1 liter of glucose and some blood. The patient became more edematous; nevertheless, the serum chloride concentration had fallen to 91.3 milliequivalents per liter. On the fifth day, diuresis began, the output being 720 cc. Thereafter it rose rapidly, reaching 6,200 cc. on the thirteenth day. As in the other cases, the early diuresis was associated with a relatively small nitrogen output, so that the serum nonprotein nitrogen level still continued to rise for several days after the onset of diuresis. The highest level, 195 mg. per hundred cubic centimeters, was obtained on the tenth day. In spite of the presence of uremia, the patient was in good enough condition to eat regular meals. There were a few moist rales in the lungs. A sudden, unexplained attack of dyspnea occurred on the eighth day. This responded to treatment with morphine and atropine. Thereafter the patient progressively improved, except for the development of a vesicovaginal fistula which made further collections of the twenty-four hour urine impossible. The serum nonprotein nitrogen level did not return to normal, until the twenty-ninth day (see table 4). Specific renal function tests showed the presence of serious tubular damage during the early phase of recovery but a complete return to normal in six months.

Case 5.—L. F., a Negro man, aged 52, who had chronic alcoholism but who was otherwise in good health, was brought into the hospital in delirium tremens after an alcoholic spree lasting three days and ending with the drinking of 4 ounces (120 cc.) of a mixture of naptha and carbon tetrachloride which had been mistaken for whisky. The patient vomited immediately and repeatedly thereafter until the time of his admission several hours later. With rapidly developing jaundice, he was regarded as having principally toxic hepatitis. He was given dextrose and vitamin B complex and encouraged to eat a high protein diet. Oliguria had persisted for three days before it was recognized that the hepatitis was relatively unimportant and that lower nephron nephrosis had developed. The patient was now given 3,000 cc. of isotonic sodium chloride solution intravenously and 3 Gm. of sodium bicarbonate every four hours by mouth. The serum chloride concentration had fallen to 78.2 milliequivalents and the serum sodium to 121 milliequivalents per liter. On each of the fifth, sixth and seventh days of oliguria, 3,000 cc. of isotonic sodium chloride solution was again administered and the bicarbonate medication continued at a dose of 4 Gm. every four hours. In addition, sodium lactate solution was administered intravenously. The urinary output reached 510 cc. on the eighth day. On the eighth day also, 500 cc. of a 2 per cent sodium chloride solution was administered but none thereafter. Rales had been present at the bases of the lungs for several days but there was no dyspnea. A remarkablly intense diuresis now occurred, the output reaching 9,900 cc. on the twelfth day. The edema rapidly disappeared, as did the nitrogenous retention, the serum nonprotein nitrogen level returning to normal by the sixteenth day. A résumé of the blood chemical changes in this patient is given in table 5. Renal function tests showed a return to normal in three months.

TABLE 4.—*Chemical Findings in Serum and Urine and Blood Pressure Changes in Case 4 (H.K.)*

Days After Onset of Oliguria	Non-protein Nitrogen, Mg./100 Cc.	Creatinine Mg./100 Cc.	Sodium, Meq./L.	Chloride, Meq./L.	Carbon Dioxide, Cc./100 Cc.	Potassium, Mg./100 Cc.	Calcium, Mg./100 Cc.	Inorganic Phosphorus, Mg./100 Cc.	Uric Acid, Mg./100 Cc.	Albumin to Globulin Ratio, Gm./100 Cc.	Urinary Volume, Cc./24 Hr.	Urinary Non-protein Nitrogen, Gm./24 Hr.	Ratio of Urinary to Serum Non-protein Nitrogen	Blood Pressure, Mm. Hg.
3	154	6.4	140	114	26		7.0	8.8	14.4	1.2/2.7	225	0.54	2.3	118/70
5	159	8.7	130	91	35	14.0				0.9/3.1	720			102/64
7	182	11.1	138	96	38	17.0	6.4	12.2	20.4	2.2/1.7	1550	5.0	1.8	106/68
9	194	11.9	144	97	34	17.0	6.6	13.3		2.9/1.7	2500	7.2	1.5	112/74
10	195	10.3	130	95	32	17.0	7.0		15.6	2.4/2.7	3075			120/80
12	178	9.5	137	97	34	21.1	6.8	14.6	14.0	2.8/2.3	6200	25.0	2.3	125/70
15	120		147	103	50	22.8			7.0	3.1/3.1	4800	26.9	4.7	
19	62	2.4	148	100	57	19.8			5.6	3.7/2.6				
22	36	1.3	145	98	54	16.8	9.6	4.6	4.0	3.4/2.5				
29	16	0.9	145	102	50	18.0	9.3	5.2		3.4/2.4				122/74

CASE 6.—H. P., a white girl 21 months of age, was admitted to the hospital in anuria, with pounding heart, jerky movements, enlarged liver and subcutaneous edema. She had been vomiting for three days. The child had been well until about a week before when stomatitis developed, for which sulfadiazine was prescribed. Two days later, a second physician gave an intramuscular injection of 0.25 cc. of bismuth sodium thioglycollate N.N.R. (thio-bismol[R]). Anuria had set in during the twenty-four hours before entrance to the hospital. The serum nonprotein nitrogen concentration was already decidedly elevated. The child was given 100 cc. of Ringer's solution and 500 cc. of glucose solution intravenously on each of the first four days. The amount of edema increased. The serum nonprotein nitrogen level was now 180 mg. per hundred cubic centimeters. Because the serum chloride was dangerously low (58.1 milliequivalents per liter), 75 cc. of 2 per cent sodium chloride solution was administered intravenously. This was increased to 150 cc. for two days and then to 175 cc. In addition, 150 cc. of sixth-molar sodium lactate solution was administered. Two hundred cubic centimeters of 10 per cent solution of a lypohilized protein hydrolysate (elamine lyophilized[R]) was also administered daily. On the eighth day of anuria a transfusion of 200 cc. of whole blood was given, without reaction. Under this regimen, the patient was clinically better, in spite of the increased edema. Vomiting had stopped, and the child was taking some food by mouth. The blood pressure had slowly risen to 130 systolic and 80 diastolic. During each of the first eleven days, only a few cubic centimeters of urine was passed. On the twelfth day, a little more was excreted, but its exact quantity could not be determined because urination was involuntary. On the thirteenth day, a recognizable diuresis set in and continued unabated until the twentieth day. The output of urine could not be determined because urination remained involuntary. By the twentieth day edema had disappeared and the child was clinically much improved. The ratio of the creatinine concentration of urine to that of serum rose during this period from 2.0 to 7.3 (table 6).

The serum nonprotein nitrogen level reached a plateau on the eighth day of the anuria which lasted for eight days. The highest serum nonprotein nitrogen concentration was 220 mg. per hundred cubic centimeters on the second day of diuresis. Chloride and sodium concentrations remained low during the entire anuric period, rising only moderately with the injection of 2 per cent sodium chloride solution. Not until the ninth day of diuresis did the chloride and sodium concentrations return to normal. The course of these and other blood constituents is shown in table 6.

Despite the persistent diuresis and the disappearance of edema, the child did not completely recover from her illness. The blood pressure, instead of continuing to fall, rose again to 160 mm. systolic about two weeks after the onset of diuresis. At this time, there were rales and dulness in the lungs, along with fever and a high white blood cell count. Penicillin was again administered for what was apparently bronchopneumonia. This illness subsided, but evidence of myocardial failure was now present, and the serum nonprotein nitrogen level which had fallen to 83 mg. per hundred cubic centimeters began to rise again, reaching 156 mg. Digitoxin U.S.P. was prescribed in doses of 0.1 mg. twice a day until digitalization occurred. The dose was then reduced to 0.05 mg. daily. Improvement occurred rapidly. With the urging of a greater water intake, the urinary output increased and the serum nonprotein nitrogen level dropped slowly again to 55 mg. per hundred cubic centimeters. At nearly four months after the onset of the illness, the patient still had a slight nitrogen retention; she was severely anemic in spite of several transfusions, and her urine still contained albumin, but no blood or

TABLE 5.—*Chemical Findings in Serum and Urine and Blood Pressure Changes in Case 5 (L.F.)*

Days After Onset of Oliguria	Non-protein Nitrogen, Mg./100 Cc.	Creatinine, Mg./100 Cc.	Sodium, Meq./L.	Chloride, Meq./L.	Carbon Dioxide, Cc./100 Cc.	Potassium, Mg./100 Cc.	Calcium, Mg./100 Cc.	Inorganic Phosphorus, Mg./100 Cc.	Uric Acid, Mg./100 Cc.	Icterus Index	Albumin to Globulin Ratio, Gm./100 Cc.	Urinary Volume, Cc./24 Hr.	Urinary Non-protein Nitrogen, Gm./24 Hr.	Blood Pressure, Mm. Hg.
2	126	6.3	.....	89	34	....	....	....	....	....	3.3/3.1	0	....	135/75
4	160	15.8	121	78	32	20.8	....	....	16.6	52	3.0/2.2	15	....	.....
6	158	17.0	128	86	33	18.0	7.5	6.6	15.2	....	2.4/2.6	205	0.42	.....
8	158	17.0	134	90	46	14.0	....	....	15.0	31	2.4/2.6	510	....	.....
10	150	17.0	141	94	53	13.5	7.2	6.9	16.0	14	2.4/2.7	2900	6.4	150/80
12	144	16.6	144	87	57	16.2	7.4	....	16.4	....	2.7/2.7	9900	26.3	.....
15	86	5.4	144	93	57	....	9.3	5.5	12.6	....	.....	5800	26.2	140/80
16	30	2.9	.....	97	55	22.7	11.8	4.7	10.8	....	.....	2550	9.4	.....
26	23	1.3	141	108	52	22.3	9.8	3.7	6.2	13	3.3/2.6	.....	....	138/76

TABLE 6—*Chemical Findings in Serum and Urine in Case 6 (H.P.)*

Days After Onset of Oliguria	Nonprotein Nitrogen, Mg./100 Cc.	Creatinine, Mg./100 Cc.	Sodium, Meq./L.	Chloride, Meq./L.	Carbon Dioxide, Cc./100 Cc.	Potassium, Mg./100 Cc.	Calcium, Mg./100 Cc.	Inorganic Phosphorus, Mg./100 Cc.	Uric Acid, Mg./100 Cc.	Albumin to Globulin Ratio, Gm./100 Cc.	Ratio of Urinary to Serum Creatinine
2	160	5.4	.....	....	....	....	....	....	....	.....	...
5	180	5.8	116	73	56	....	....	....	....	2.69/1.89	....
7	190	8.7	109	58.1	38	17.2	6.6	6.5	13.6	2.44/1.65	....
9	205	11.4	122	74.0	32	16.9	....	....	15.2	2.34/1.63	2.3
13	211	10.4	134	83	42	....	9.8	7.9	16.2	2.49/1.16	2.3
14	220	....	.....	86	....	....	....	....	....	.....	....
17	196	....	.....	96	....	....	....	....	16.2	.....	....
19	147	....	.....	100	41	....	....	8.5	....	3.47/1.67	....
24	93	4.1	142	109	27	....	....	....	....	....	5.1
26	83	3.6	142	111	29	....	....	7.1	....	....	8.3
33	156	....	141	105	22	....	....	....	....	....	....
93	55	...	141	100	30	18.5	9.2	6.0	....	.....	....

casts. Whether this renal lesion was temporarily or permanent and whether it signified either an end result of the lower nephron nephrosis or the concomitant existence of glomerulonephritis cannot at this time be determined. Unfortunately, the continued illness and the technical difficulties with urine and blood collections made the determination of specific renal function tests impossible.

COMMENT

The clinical pictures in these cases were similar to each other in many respects. No patient had a previous history of renal or vascular involvement. A shocklike state was present in all cases, except possibly that of carbon tetrachloride poisoning. Oliguria was manifest in one to three days following the initial insult and persisted despite all measures to promote urinary output. However, there was always some urine excreted, and this appeared to us to be of diagnostic and prognostic significance. The specimens passed were slightly acid or neutral in reaction, had a specific gravity near 1.010 and contained a few red and white blood cells and casts. In 2 cases, heme casts were recognizable after the second day of oliguria.

The duration of oliguria varied from five to thirteen days. It was recognized that once the excretion rate had exceeded 500 cc. per day in adults, it rose rapidly, reaching several thousand cubic centimeters per day in a few days. In case 5, an output of 9,900 cc. was achieved and was associated with a rapid return to normal not only of the chemical composition of the blood but also of renal function.

Hypertension was absent at the beginning in all cases. In fact, the blood pressure was usually at the shock level. But as the oliguria continued, the blood pressure rose slowly until at the time of maximal retention it was 150 to 180 mm. systolic and about 100 diastolic. It returned to normal within a few days after diuresis had set in and long before the retained excretory products had been removed. Thus, the elevated blood pressure appeared to be related to renal blood flow rather than to retention of toxic products.

Edema was variable in degree and location. It occurred early in all cases and was associated with a rapid drop in serum protein concentration. Bloating of the face was seen as in acute glomerulonephritis, but there was no encephalopathy and no abnormality of the fundi. A few rales could be heard in the lungs in the first days, but these did not increase or become associated with dyspnea, except in the fatal case in which there was terminal hydrothorax and edema of the lungs. In the other 5 cases edema disappeared rapidly with diuresis. Since the serum protein concentration rose rapidly to normal after the disappearance of the edema, it was apparent that the lost serum protein never left the body but had disappeared in the extracellular fluid during the original shock.

The usual symptoms of uremia were slow to develop. Vomiting was much less marked than expected. Usually the patients could take food by mouth well. Excessive perspiration and liquid stools were frequently severe. Torpor and drowsiness were present but were not severe. Hemorrhagic tendency was seen only in the 1 fatal case. Uremic pigmentation did not develop.

The progressive development of uremia can readily be seen in tables 1 and 6. Nonprotein nitrogen, urea nitrogen and creatinine concentrations showed a parallel rise. Phosphate was similarly retained, but the rise was apparently checked by injections of calcium. The serum calcium concentrations tended to be low in association with the high phosphate and low serum protein concentrations. In the 3 cases in which it was studied uric acid concentration was strikingly elevated to a level beyond that usually seen in the early uremia. This level declined to normal much more slowly than that of the other nitrogenous constituents. Serum potassium rose considerably only in the fatal case. Phenol and indican contents were found elevated but not nearly as high as during long-standing insufficiency.

Serum chloride and sodium concentrations were lower than normal in spite of the presence of edema. This was probably a manifestation of the loss of the mechanism in the kidney for regulating the excretion of water ingested (or formed) in excess of that required to produce an isotonic solution of the ingested sodium and chloride. Even when isotonic sodium chloride solution was administered, the amount of edema fluid increased, but the serum chloride and sodium levels still remained below normal. When 2 per cent sodium chloride solution was given, these concentrations tended to rise more rapidly. As soon as diuresis became established, serum chloride and sodium concentrations rose rapidly to normal because of the excretion of urine relatively low in chloride and sodium. In none of these cases, however, were the abnormally high levels of sodium and chloride reached during recovery as reported by Leutscher and Blackman[19] in 3 cases which followed sulfonamide anuria.

The tendency for the serum nonprotein nitrogen concentrations to level off in the later days of oliguria in spite of the continued intake of protein is believed due to the expansion of extracellular fluid volume deliberately accomplished. This phenomenon, in addition to the raising of the electrolyte levels toward normal, is probably responsible for the relatively mild uremic symptoms in these patients. We feel that these factors helped prolong the life of the patients until the natural recovery of

19. Leutscher, J. A., and Blackman, S. S., Jr.: Severe Injury to Kidneys and Brain Following Sulfathiazole Administration: High Serum Sodium and Chloride Levels and Persistent Cerebral Damage, Ann. Int. Med. **18**:741, 1943.

the kidneys was far enough along to reverse the retention of excretory products.

SUMMARY

Six patients with lower nephron nephrosis from a variety of causes were managed by a regimen that included a deliberate induction of edema of nearly normal electrolyte composition for the purpose of diluting the accumulating intoxication products. Other measures were designed to keep the patient in a good state of nutrition. Five of the 6 patients recovered; the sixth died in uremia and heart failure five days after the onset of diuresis. Four of the recovered patients had complete restoration to normal renal function. One patient, a child 2 years of age, still had renal insufficiency nearly four months after the onset of diuresis.

Observations on the clinical course of these patients and the progressive changes in serum and urinary chemical findings lead to the belief that the major lesions are diminshed renal blood flow and loss of specific function of the lower portion of the nephron. Recovery appears to be initiated by an increase in effective renal blood flow and continued more slowly by improvement in specific function of the damaged tubules.

629 South Wood Street (12).

Mrs. Catherine Nobe performed the chemical analyses.

HYPERCHLOREMIC ACIDOSIS AND NEPHROCALCINOSIS

The Syndrome of Pure "Lower Nephron" Insufficiency

EZRA M. GREENSPAN, M.D.
WASHINGTON, D. C.

IN RECENT years the term "nephrocalcinosis" has been used to designate cases of bilateral generalized calcification within the renal parenchyma. In many instances little importance has been attached to the particular anatomic position of the multiple renal calcifications. However, several observers[1] called attention to a few rare cases of idiopathic nephrocalcinosis in which numerous submiliary, symmetric bilateral calcifications were confined to the renal pyramids. Special significance was attributed to the localization of the renal calcifications in these cases, since they were associated with a unique form of chronic renal failure. In this syndrome renal dysfunction was characterized by severe, intractable chronic hyperchloremic acidosis of months or years' duration, together with pronounced chronic polyuria, polydipsia, asthenia and either osteoporosis (adults) or "renal rickets" (children). Several therapeutic measures directed against this metabolic disorder resulted in prolonged symptomatic improvement. Lack of treatment predisposed to further deposition of calcium in the basement membrane and cells of the distal tubules and collecting tubules.

On roentgenologic examination the calcifications usually are visible as clumps of submiliary, stippled, cauliflower-like calcium deposits in

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From the medical service of Dr. I. Snapper, The Mount Sinai Hospital, New York.

1. (*a*) Albright, F.; Consolazio, W. V.; Coombs, F. S.; Sulkowitch, H. W., and Talbott, J. H.: Metabolic Studies and Therapy in a Case of Nephrocalcinosis with Rickets and Dwarfism, Bull. Johns Hopkins Hosp. **66**:7-33 (Jan.) 1940. (*b*) Butler, A. M.; Wilson, J. L., and Farber, S.: Dehydration and Acidosis with Calcification of Renal Tubules, J. Pediat. **8**:489-499 (April) 1936. (*c*) Lightwood, R., cited by Butler, Wilson and Farber.[1b] (*d*) Rule, C., and Grollman, A.: Osteo-Nephropathy: A Clinical Consideration of "Renal Rickets," Ann. Int. Med. **20**: 63-74 (Jan.) 1944. (*e*) Boyd, J. D., and Stearns, G.: Late Rickets Resembling Fanconi Syndrome, Am. J. Dis. Child. **61**:1012-1022 (May) 1941. (*f*) Baines, G. H.; Barclay, J. A., and Cooke, W. T.: Nephrocalcinosis Associated with Hyperchloremia and Low Plasma Bicarbonate, Quart. J. Med. **14**:113-123 (April) 1945. (*g*) Payne, W. W.: Case Report: Nephrocalcinosis Associated with Hyperchloraemia, Proc. Roy. Soc. Med. **39**:133-134 (Jan.) 1946.

the renal medullas. These calcifications outline the calyceal systems of both kidneys perfectly, despite the absence of calculi in the calyxes or pelves (see figures 1 and 2). Cases of scattered renal calcifications of irregular size or disposition, as well as cases of hyperparathyroidism (primary or secondary) with irregular renal and pelvic calcifications, are easily differentiated from this form of idiopathic nephrocalcinosis, since they almost invariably manifest different biochemical abnormalities. Among the numerous cases of renal calcification in primary hyperparathyroidism only 1 instance was reported[1b] in which the lesions apparently were so well localized in the distal tubules as to give rise to chronic hyperchloremic acidosis, in association with the general metabolic features of hyperparathyroidism.

This presentation is based on the observation and treatment of this unusual biochemical and clinical syndrome occurring in a man with nephrocalcinosis of indefinite origins, associated with severe chronic hyperchloremic acidosis and an unusual form of renal failure. The development of this biochemical syndrome has not heretofore been reported in an adult. Among infants the syndrome was first recognized by Lightwood[1c] in an unpublished paper read before the British Pediatric Association in 1935. In the following year, Butler, Wilson and Farber[1b] described in detail clinical and pathologic observations on 4 infants who died with a chloride acidosis resistant to therapy. These infants had not had excessive diarrhea, vomiting or infection. Nevertheless, they demonstrated evidences of clinical dehydration soon after birth, associated with intractable hyperpnea, acidosis and polyuria. These signs persisted for many weeks despite intensive administration of salt, food of high caloric value and fluids. At autopsy examination, numerous bristle-like calcium deposits were observed in the pyramids, whereas the cortices, calyxes and ureters were relatively normal. Microscopic deposits of calcium were observed in the distal tubules between the basement membrane and the epithelial cells. There was no evidence that the calcium deposition was secondary to degeneration of any specific renal element. No metastatic calcification or abnormality of the parathyroid glands was observed in these patients.

In the same report, Butler, Wilson and Farber[1b] made brief reference in a footnote to 2 patients of more advanced age, one a 10 year old boy with idiopathic nephrocalcinosis and hyperchloremic acidosis, associated with "renal rickets," and the other a man with primary hyperparathyroidism, nephrocalcinosis and hyperchloremic acidosis. A single detailed case study was later reported by Albright and his collaborators.[1a] Their patient was a puberal girl with nephrocalcinosis, hyperchloremic acidosis, rickets and dwarfism. The unusual features of the renal insufficiency in this patient were admirably and completely demonstrated by careful

balance studies. An excellent therapeutic result was obtained by the use of the regimen employing citric acid and sodium citrate, devised by Shohl[2] and Shohl and Butler[3] for the treatment of experimental rickets (v. i.). Recently, Rule and Grollman,[1d] Payne[1g] and Boyd and Stearns[1e] described single cases of this syndrome in adolescents who, without exception, had symptoms since early childhood. Varying degrees of improvement were witnessed after treatment with citrate mixtures. The only adult patient thus far reported on was a 29 year old woman observed by Baines, Barclay and Cooke[1f] for several years. She was known

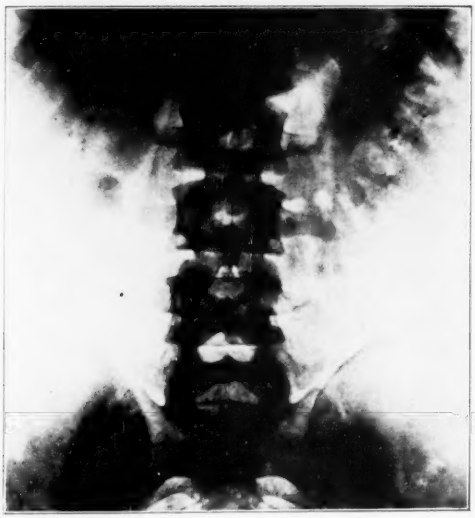

Fig. 1.—Roentgenogram showing nephrocalcinosis. This patient with chronic hyperchloremic acidosis has bilateral, symmetric, stippled calcifications confined to the renal pyramids.

to have had excessive polyuria and polydipsia since the age of 10 years. Typical hyperchloremia, low plasma bicarbonate and nephrocalcinosis were reported, associated with renal insufficiency similar to that to be described later. No skeletal changes were noted on roentgenologic examination despite five years of known acidosis. This observation con-

2. Shohl, A. T.: Effect of Acid-Base Content of Diet upon Production and Cure of Rickets with Special Reference to Citrate, J. Nutrition **14**:69-83 (July) 1937.

3. Shohl, A. T., and Butler, A. M.: Citrates in Treatment of Infantile Rickets, New England J. Med. **220**:515-517 (March 23) 1937.

trasted with the previous reports on children in whom skeletal changes characteristic of "renal rickets" occurred. Death of this patient was precipitated by an unusually severe reaction following a course of sulfathiazole in the usual doses.

The etiologic factors in this syndrome have been variously postulated as congenital dysfunction of the distal tubules,[1a] congenital tubular precipitates, mild chronic diabetes insipidus, drug toxicity,[1f] chronic pyelonephritis[4] and "perversion of the entire electrolyte system of the body."[1e] The results of biochemical studies and the case history of a man are presented whose symptoms appeared to develop shortly after treatment of pneumonia with standard doses of sulfathiazole. Considerable

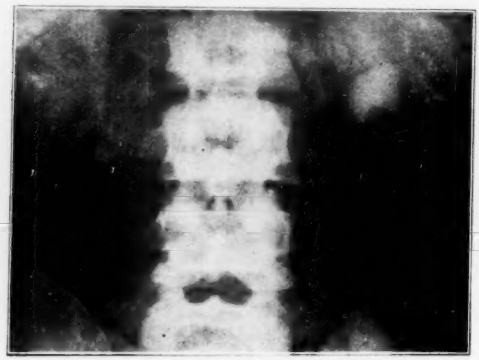

Fig. 2.—Intravenous pyelogram of patient in figure 1. Note excellent dye concentration.

improvement in the hyperchloremic acidosis occurred during three years of treatment, but there was no alteration in the nephrocalcinosis or the major aspects of the renal insufficiency. The occurrence of chronic hyperchloremic acidosis and nephrocalcinosis in an adult subsequent to sulfonamide therapy suggests that drug toxicity may play an etiologic role, in addition to the other factors postulated by previous authors.

REPORT OF A CASE

A 44 year old man was admitted for the first time to Mount Sinai Hospital in November 1944, with the chief complaint of fatigue and progressive weakness of three years' duration. The patient had been well until April 1941, when he

4. Peterman, M. G.: Chronic Pyelonephritis with Renal Acidosis, Am. J. Dis. Child. **69**:291-294 (May) 1945.

was admitted to a suburban hospital for an episode of "lobar pneumonia." He was treated with a total of 195 grains (12.6 Gm.) of sulfathiazole, administered orally over a five day period. Although definite toxicity was not observed, examination of the urine during therapy revealed occasional hyaline and granular casts. An uneventful recovery followed the pneumonia, but shortly thereafter the patient noted the onset of progressive polyuria, polydipsia and nocturia, associated with a craving for salt, spicy foods and beer. He was unable to regain a 25 pound (11.3 Kg.) loss in weight and noted persistent progressive fatigue with moderate dyspena on exertion. He observed the appearance of slight edema of the ankles after periods of standing.

In 1942 and 1943, the patient had two other attacks of pneumonia. The former was treated with 105 grains (6.8 Gm.) of sulfathiazole, the latter with

Fig. 3.—Severer nephrocalcinosis in a patient without evidence of hyperchloremic acidosis.

135 grains (8.9 Gm.) of sulfadiazine. There were no signs of sulfonamide toxicity. Progressive asthenia after the third bout of pneumonia made it impossible for the patient to continue his work as a machinist. He consulted a local physician after three years of persistent fatigue and polyuria. Past history revealed the fact that results of urinalysis were normal in 1938. A mild hypotension had been known to be present. In addition, over five years approximately six episodes of localized purpura were observed to occur bilaterally between the ankles and knees. Residual slaty brown pigmentation remained. The patient had undergone an appendec-

tomy uneventfully in 1940, four years prior to admission to the Mount Sinai Hospital. There was no history of stunted growth, fractures, renal stones, ingestion of alkali, gastric disturbances, prolonged vomiting, administration of vitamin D or hepatic disease.

Because of the history of fatigue, weakness and hypotension, the patient's family physician suspected the presence of adrenal cortical hypofunction (Addison's disease). A roentgenogram of the abdomen, to show possible calcification of the adrenal glands, revealed extensive deposits of calcium in the kidneys (figs. 1 and 2). Results of a biochemical study, performed by Dr. I. Rudnikoff, of Yonkers, N. Y., were not suggestive of hyperparathyroidism. Because of the bizarre clinical syndrome, the patient was admitted to Mount Sinai Hospital, on Nov. 18, 1944, for further study.

Fig. 4.—Intravenous pyelogram of patient in figure 3.

Physical Examination.—The patient was a thin, poorly developed, alert, 44 year old white man, not appearing ill. Temperature, pulse and respirations were normal. Head and neck were not remarkable except for one semiformed spider angioma of the right malar eminence, known to be present for many years. A few small, shotty cervical nodes were palpable. Heart and lungs were normal. Blood pressure measured 110 mm. of mercury systolic and 70 mm. diastolic. The edge of the liver was palpable at the costal margin and was soft, smooth and thin. The skin of both legs, between instep and knees, was discolored with a dark, slaty brown pigmentation, completely coalescent. Examination otherwise showed nothing remarkable.

Laboratory Studies.—Blood: Examination of peripheral blood revealed 74 per cent hemoglobin (Sahli), 4,100,000 red blood cells and 9,000 white blood cells per cubic millimeter, with a normal differential count. Bone marrow (sternum) showed nothing remarkable on examination. Results of the tourniquet test were normal. Bleeding time was 2 minutes and clotting time (Lee-White), 5 minutes.

Urinalysis: The urine showed a specific gravity of 1.010 and a p_H of 7 to 7.5, with a faint trace of albumin and no reducing substances. Microscopic examination of centrifuged sediment revealed an occasional white blood cell per high power field. Cultures of the urine persistently yielded no pathogenic organisms except for Staphylococcus albus on one occasion, probably the result of a contaminant. Inoculation of a guinea pig revealed no acid-fast bacilli after eight weeks. Excretion of phenolsulfonphthalein was 35 per cent in the first hour and 5 per cent in the second hour. Reaction to the Sulkowitch test was normal. The Fishberg concentration test for renal function showed a specifc gravity of 1.012; the result of the dilution test was 1.004. Urea clearance was 60 per cent normal. The glucose threshold was 170 mg. per hundred cubic centimeters (normal). Creatinine clearance was 90 cc. per minute.

Blood Chemistry: Urea nitrogen measured 16 mg., glucose, 80 mg., and creatinine, 1.55 mg., per hundred cubic centimeters There were 140 milliequivalents of sodium and 116 milliequivalents of serum chloride (679 mg. per hundred cubic centimeters expressed as sodium chloride). Carbon dioxide-combining power was 28 volumes per cent. Serum calcium was 9 mg. and serum phosphorus, 1.8 mg. per hundred cubic centimeters, while the alkaline phosphatase value was 9 King-Armstrong units. Protein totaled 7.8 Gm., albumin, 3.4 Gm. and globulin, 4.14 Gm., per hundred cubic centimeters. The test using solution of formaldehyde U.S.P. gave a positive reaction for globulin. Cholesterol measured 220 mg. per hundred cubic centimeters. The glucose tolerance test (microtechnic) gave results of 130, 190, 200, 170 and 100 mg. per hundred cubic centimeters. The blood uric acid level was 4.2 mg. per hundred cubic centimeters (Folin-Wu). The erythrocyte sedimentation rate was 105 mm. per hour (Westergren). The oral test yielded excretion of 3.6 Gm. of hippuric acid. The sulfobromophthalein sodium U.S.P. test (2 mg. per kilogram of body weight) showed less than 5 per cent retention after one-half hour. The cephalin flocculation test gave a 2 plus reaction (normal). Serum cryoglobulins were absent.

Roentgenographic Examination: The interpretation of the roentgenograms by Dr. Marcy Sussman, chief roentgenologist, was as follows:

A few indefinite areas of decreased density are seen in the region of the greater tuberosity of the right humerus, the upper aspect of the internal condyle of the right femur and the lower lateral aspect of the right ilium. The bones of the calvarium show slight mottling. The kidneys are normal in size, shape and position. In the kidneys, there are numerous dense, small calcium deposits present symmetrically in the pyramids. Minimal dilatation of the pelves on both sides is present. There is no abnormality of the heart or lungs. Dental roentgenograms reveal slight ground-glass appearance and poorly defined trabeculae. The absence of teeth prevents a description of the lamina dura.

Electrocardiographic examination showed no significant abnormality.

TABLE 1.—*Blood Chemistry Data on Patient With Hyperchloremic Acidosis and Nephrocalcinosis*

Date		Chlorides,		Carbon Dioxide Content, Volumes %	Urea, Mg./100 Cc.	Sodium, mEq./L.	Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Alkaline Phosphatase, King-Armstrong Units
		NaCl, Mg./100 Cc.	mEq./L.						
11-19-44	Admission	680	116.2	28.0	16	....	9	2.8	9
11-26-44	Ward diet	690	118.1	40.1	....	140	....	....	....
12-2-44	Bauer-Aub diet plus	690	118.1	37.8	20	138	....	....	12
12-7-44	6 Gm. ammonium chloride every day	690	118.1	30.1	....	....	....	....	....
12-11-44	Ward diet	650	111.4	33.6	....	....	....	....	....
12-12-44	Ward diet plus 8 Gm. sodium chloride	660	112.9	....	26	....	9.5	2.5	....
		682	116.3	30.1	....	....	....	....	....
12-19-44	Ward diet	661	113.0	34.7	21	....	9.5	2.1	....
12-20-44									
12-23-44		655	112.1	40.1	....	143	....	....	....
2-5-45	Citrate buffer mixture	650	111.4	42.0	15	140	10.7	2.7	15
2-17-45	plus 1 Gm. calcium	590	101.1	49.0	18	142	....	....	....
4-7-45	gluconate daily	608	103.7	46.?	17	....	10.7	2.9	11.5
6-7-45		630	107.0	42.7	16	....	9.7	2.3	9
10-26-45		632	107.1	42.9	11	....	9.0	2.3	....
11-20-45	Citrate mixture	660	112.9	38.0	22	138	9.0	2.2	11
11-26-45	withheld								
1-3-46									
1-5-46	Citrate mixture	632	107.1	39.6	....	....	10.6	1.8	10
1-15-46	withheld	680	116.2	31.0	26	....	....	....	....
1-16-46	Citrate mixture	620	106.1	50.1	17	....	9.7	1.2	8
3-25-46	resumed								
12-4-47	Citrate mixture intermittently	638	108.7	....	17	....	10.5	....	10

TABLE 2.—*Data on Renal Function in Patient with Hyperchloremic Acidosis and Nephrocalcinosis*

Date		Blood Urea, Mg./100 Cc.	Calcium Excretion, Mg./Day	Chloride Excretion, Gm./Day	pH	Specific Gravity	Protein	Results of Microscopic Study	Results of Renal Function Tests
11-19-44	Admission	16	437	10	7.5	1.010	+	Occasional white blood cell	Phenolsulfonphthalein excretion, 40%
12-1-44	Bauer-Aub diet plus	20	438	12.5	7.5	1.010	++	Occasional white blood cell	
12-7-44	6 Gm. ammonium chloride	....	292	14.0	....	....	....	Occasional red blood cell	Urea clearance, 60%
		....	382	8.5	....	....	....		
12-11-45	Ward diet	....	....	....	7.5	1.010	0	Negative	240 mg. protein/100 Cc. urine every day (Esbach)
2-17-45	Treated*	18	136	....	7.0	1.010	Faint trace	Occasional white blood cell	Phenolsulfonphthalein excretion, 50%; urea clearance, 67%
11-26-45	Untreated (6 days)	22	312	...	7.5	1.010	0	Negative	Creatinine clearance, 90 cc./min.
1-15-46	Untreated (12 days)	26	396	....	7.0	1.010	0	Negative	Ammonia/urea nitrogen=16/1,200 Urea clearance, 76%
3-25-46	Treated (6 weeks)	17	186	....	7.5	1.010	0	Occasional white blood cell	
12-4-47	Intermittently treated (1¼ yr.)	17	....	....	Alkaline	1.010	++	2 to 3 white blood cells; occasional red blood cell	

*Treatment consisted of diet poor in salt, 16 Gm. citric acid, 12 Gm. sodium citrate and 1 Gm. calcium gluconate orally each day.

COMMENT

The patient was studied during periods of oral ingestion of an acid salt (ammonium chloride), a neutral salt (sodium chloride) and an alkaline buffer mixture (v. i.) which was subsequently used for treatment. It was desired thereby to compare the patient's responses with those described by Albright and associates[1a] in a similar case of hyperchloremia, acidosis and nephrocalcinosis. The detailed biochemical studies are summarized in the tables and chart. Because of the unusually benign and chronic nature of the patient's hyperchloremic acidosis and renal insufficiency, studies were performed intermittently over a one and one-

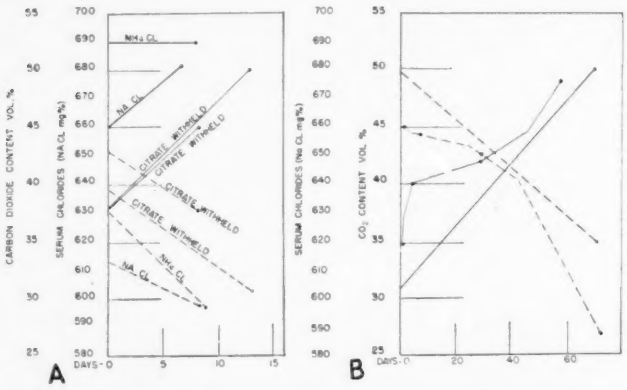

Fig. 5.—Chart *A* shows aggravation of hyperchloremic acidosis by oral administration of supplements of several salts: sodium chloride, 6 Gm. per day, and ammonium chloride, 8 Gm. per day, and withdrawal of the citrate mixture, which affected the serum chloride and plasma bicarbonate levels. The solid lines indicate serum chloride levels and the broken lines carbon dioxide content. *B* shows correction of hyperchloremic acidosis by oral administration of solutions of citric acid and sodium citrate to a patient with chronic hyperchloremic acidosis and nephrocalcinosis. The serum chloride and plasma bicarbonate levels were affected. The solid lines indicate carbon dioxide content and the broken lines serum chloride level.

half year period before any definite conclusions were made. After three years, there was no perceptible alteration or progressive change in the essential biochemical and clinical findings.

The most striking metabolic abnormality on admission to the hospital was severe acidosis (carbon dioxide-combining power, 26 volumes per cent), associated with a serum chloride value of 680 mg. per hundred cubic centimeters (sodium chloride) or 116 milliequivalents per liter. After several days on the ward diet, which was relatively poor in salt and chloride, the carbon dioxide level increased slightly. An attempt

was then made to determine whether ingestion of ammonium chloride would lead to chloride retention. A moderate fall in the carbon dioxide content ensued, but there was no further increase in the chloride level. During a period of ingestion of excess sodium chloride, the acidosis remained unaffected and there was a slight further increase in the already high chloride level. It was noteworthy that the aggravation of the preexisting acidosis by neutral salt (sodium chloride) was similar to that observed by Albright and associates.[1a] These observations demonstrate the failure of the normal mechanism for the excretion of chloride and the absorption of base. This abnormality is similar in many respects to that seen in experimental and clinical diabetes insipidus[5] in which the inability to handle Na^+ and Cl^- often results in hyperchloremic acidosis.

The patient responded well to the regimen originally designed by Shohl[2] to create a state of intestinal acidosis and humoral alkalosis in the treatment of experimental rickets[6] induced by acidosis or retention of phosphorus. It was modified slightly to include (*a*) restricted intake of sodium chloride, (*b*) daily ingestion of 120 cc. of a solution containing 16 Gm. of citric acid and 12 Gm. of sodium citrate and (*c*) 1 Gm. of calcium gluconate daily. The citrate mixture created favorable conditions for the absorption of calcium salts in the upper part of the gastrointestinal tract. Humoral alkalosis was induced by the sodium citrate, which supplied free base on oxidation of the citrate in the body. With this regimen there was less need for calcium excretion, since the tendency toward alkalosis facilitated deposition of calcium in the bones. In the patient presented herewith the daily calcium excretion fell from approximately 400 to 150 mg. despite the fact that the acidosis, which promoted calciuria, was not entirely eliminated.

Throughout the entire period of observation the patient showed low normal serum calcium levels (9.0 to 10.7 mg. per hundred cubic centimeters) and subnormal inorganic phosphorus levels (1.2 to 2.8 mg.) which were interpreted as evidence of calcium-phosphaturia and sodium-phosphaturia, based on the inability of the distal tubules to reabsorb phosphate and bicarbonate anion. The hypophosphatemia and phos-

5. Butler, A. M.; Harper, E. A., and Carey, B. W., Jr.: Excretion of Sodium Chlorides in Normal Persons and in Persons with Nephritis and Diabetes Insipidus, Am. J. Dis. Child. **46**:1459-1460 (Nov.) 1933.

6. Hamilton, B., and Dewar, M. M.: Effect of Citrate and Tartrate on Experimental Rickets, Am. J. Dis. Child. **54**:548-556 (Sept.) 1937.

phaturia could be differentiated from that observed in early hyperparathyroidism by the low or normal blood calcium level over a long period of observation in a patient concomitantly showing pronounced renal impairment (isosthenuria, fixed urinary alkalosis and such conditions) and chronic acidosis.

The minimal osteoporotic changes seen in this patient after four years of chronic acidosis were not considered remarkable. A similar pattern was reported by other observers[1f] in an adult patient. This similarity bespeaks the large calcium reserve possessed by adults. However, "renal rickets" and dwarfism developed more rapidly when the same renal lesion occurred in growing children.[7] Two months after treatment on the citrate regimen a slight elevation of the alkaline phosphatase occurred. This probably represented a deviation of calcium to the bones and an increase in osteoblastic activity. It was associated with a decline in the hyperchloremic acidosis, diminution in calcinuria and a generally improved clinical condition.

The normal sodium levels (138 to 143.4 milliequivalents per liter) in a patient with isosthenuria and urinary alkalosis were similar to those in other cases of hyperchloremic acidosis. The great losses of sodium via the kidney could apparently be replaced, provided no other loss of sodium occurred through damaged capillary beds elsewhere in the body. This contrasted sharply with the blood hyponatremia and tissue hypernatremia usually observed in nephritic uremia, a disorder in which there is a general deviation of salts from the capillary beds into the tissue spaces and the gastrointestinal tract.[8]

The principal action of the regimen including sodium citrate and citric acid in this patient was to elevate the plasma level of bicarbonate from 30 to 45 volumes per hundred cubic centimeters and to depress the chlorides from 690 to 610 mg. per hundred cubic centimeters (118 to 104.5 milliequivalents per liter). Most remarkable was the apparent lack of progression in the renal lesion during three years of treatment and observation. Symptomatically, the citrate buffer mixture produced sustained improvement in the incapacitating symptoms of extreme weakness and malaise. On three separate occasions the withdrawal of treatment produced prompt clinical relapse manifested by polyuria, polydipsia, dyspnea, fatigue and inability to perform moderately strenuous labor as a machinist. Clinical remissions with treatment paralleled the improvement in biochemical abnormalities.

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7. Albright and others.[1a] Butler and others.[1b] Rule and Grollman.[1d] Boyd and Stearns.[1e]

8. Peters, J. P.; Wakeman, A. M., and Lee, C.: Total Acid-Base Equilibrium of Plasma in Health and Disease, J. Clin. Investigation **6**:551-557 (Feb.) 1929.

PHYSIOLOGIC MECHANISM OF DISTAL TUBULE INSUFFICIENCY

It seemed likely that this case presented a bizarre form of chronic renal insufficiency involving principally, if not only, the lower portions of the nephrons without significantly affecting the glomeruli or the proximal tubules. Glomerular function appeared to be relatively intact, as manifested by normal urea nitrogen, hypophosphatemia, normal organic acid fraction and moderate impairment of urea clearance (60 to 76 per cent) and of creatinine clearance (90 cc. per minute). The normal glucose threshold, fair excretion of phenolsulfonphthalein (40 per cent) and good visualization with iodopyracet injection U.S.P. ("diodrast") (fig. 2) indicated functionally intact proximal tubles.

If one may apply to man the microchemical studies of tubular urine in the amphibian kidney performed by Walker and Hudson,[9] the principal function to be assigned to the proximal convoluted tubules is reabsorption of water and electrolytes in isotonic solution. They showed that four fifths of phosphate and water is reabsorbed in the proximal tubule without any change in p_H. Since no change in p_H occurs, it was assumed that carbonic acid and bicarbonate are absorbed freely across the epithelium of the proximal tubule. Concentration of urine and p_H adjustment are stated to occur in the distal tubule by selective absorption of water, by the production of ammonia and by the excretion of titratable acid.

In the production of acid urine, ammonium salts obviously play no direct role. Normally, between 5 and 10 per cent of urinary nitrogen is in the form of ammonia, produced in the distal tubules. Approximately 20 to 50 milliequivalents of fixed base is saved daily by this mechanism. In this patient, there was diminution in ammonia production to only 1.3 per cent of urinary nitrogen, even after acidifying salt (ammonium chloride) feedings. Although Albright and associates[1a] postulated a reduced ammonia production as one of two possible mechanisms which may be responsible for the syndrome of hyperchloremic acidosis, it is difficult to understand how it may play a part in the major defect in this case, namely, the inability to produce an acid urine. The inability to produce ammonia would merely result in an extra daily urinary loss of a relatively small amount of base.

Until recently, it was assumed that the production of an acid urine could be accounted for by the conversion of dibasic phosphates to monobasic phosphates, i.e., by the rate of selective sodium reabsorption and

9. Walker, A. M., and Hudson, C. L.: Role of Tubule in Excretion of Inorganic Phosphate by Amphibian Kidney, Am. J. Physiol. **118**:167-173 (Jan.) 1937.

phosphate excretion. However, Pitts and Alexander[10] and Pitts and Lotspeich[11] recently showed that the quantity of titratable acid in the urine may at times far exceed the quantity of available acid filtered through the glomeruli. Under conditions of maximal stimulation of the renal acidifying mechanism in dogs, excretion of monobasic phosphate could account for only 11 per cent of observed urinary acid.[10] It was therefore necessary to postulate[10] a "tubular mechanism for the transportation of acid from the postglomerular blood into the tubular lumen." A direct exchange of hydrogen ions for base in the tubular urine was assumed to occur across the distal tubule segment from the only possible source of such ions—carbonic acid. Since the rate of hydration of carbon dioxide to form carbonic acid is known to be governed by the enzyme, carbonic anhydrase,[12] any substance inhibiting or destroying enzyme proteins may interfere with the mechanism of hydrogen ion transportation from the postglomerular blood into the tubular urine. In such circumstances urinary alkalosis has been produced, even in the presence of systemic acidosis,[13] a situation similar to that seen in this patient.

The presence of chronic hyperchloremia in states of acidosis is rare in nephritic uremia,[8] and was not reported in cases of nephrocalcinosis principally involving the proximal convoluted tubules (see table 4). The hyperchloremia (118 milliequivalents per liter) in this patient seemed to reflect satisfactory chloride reabsorption compared with a decided impairment of reabsorption of the other principal anions—bicarbonate and phosphate—which are absorbed normally in the distal portions of the nephron. It is significant that the acidification of urine in amphibian kidneys occurs in a small discrete segment constituting only one fifth of the total length of the distal tubule,[14] whereas chloride and

10. Pitts, R. F., and Alexander, R. S.: The Nature of the Renal Tubular Mechanism for Acidifying the Urine, Am. J. Physiol. **144**:239-254 (July) 1945.

11. Pitts, R. F., and Lotspeich, W. D.: Bicarbonate and the Renal Regulation of Acid Base Balance, Am. J. Physiol. **147**:138-154 (Sept.) 1946; Factors Governing the Rate of Excretion of Titratable Acid in the Dog, ibid. **147**:481-492 (Nov.) 1946.

12. (*a*) Mann, T., and Keilin, D.: Sulphanilamide as a Specific Inhibitor of Carbonic Anhydrase, Nature, London **146**:164-165 (Aug. 3) 1940. (*b*) Davenport, M. W.: The Inhibition of Carbonic Anhydrase and of Gastric Acid Secretion by Sulfanilamide, Am. J. Physiol. **129**:505-514 (June) 1940. (*c*) Roughton, F. J. W.; Dill, D. B.; Darling, R. C.; Graybiel, A.; Knehr, C. A., and Talbott, J. H.: Some Effects of Sulfanilamide on Men at Rest and During Exercise, ibid. **135**:77-87 (Dec.) 1941.

13. McChesney, E. W.; Sprague, K. D., and Marshall, I. H.: Effect of Sulfanilamide on Acid-Base Balance, J. Lab. & Clin. Med. **26**:1154-1159 (April) 1941.

14. Montgomery, H., and Pierce, J. A.: Site of Acidification of Urine Within Renal Tubule in Amphibian Kidney, Am. J. Physiol. **118**:114-152 (Jan.) 1937.

sodium reabsorption proceeds throughout the length of the entire distal tubule.[15] By means of dye studies,[14] the acidification segment of amphibian tubules was observed to be located somewhat nearer the distal than the proximal end of the distal tubule. These observations may not be directly applied to the human tubules because of the presence of the loop of Henle, which has not been studied with microchemical methods. It is believed, however, that chloride reabsorption occurs as a principal function of the loop of Henle,[15] and that the acidification of human urine probably occurs somewhat distally in the convoluted tubules. If these conclusions are applied to man, the hyperchloremia in this patient may be explained as a manifestation of discrete lower nephron insufficiency. When the acidification segment and the more distal portions of the distal tubules and collecting tubules are selectively calcified, chloride reabsorption may remain relatively less impaired than the reabsorption of other anions. This interpretation is supported by the ob-

TABLE 3.—*Syndrome of Pure Distal Tubule Insufficiency*

Blood	Hyperchloremia Acidosis Isonatremia Hypophosphatemia Hypocalcemia or isocalcemia Absence of azotemia
Upper nephron (Minimal impairment)	Urea clearance Phenolsulfonphthalein excretion Creatinine clearance Iodopyracet visualization (clearance)
Lower Nephron (Total impairment)	Fixed urinary alkalosis Isosthenuria Deficient production of ammonia Polyuria
Osseous system	Negative calcium balance "Renal rickets" in adolescents Osteoporosis in adults

servations of necrosis and calcification confined to the collecting tubules and distal tubules in infants who died with chronic hyperchloremic acidosis.[1b] On the other hand, a chronic hyperchloremic acidosis would be expected to be absent in extensive cases of calcinosis involving both the proximal and the distal nephron. Such have been the observations in cases of extensive nephrocalcinosis studied recently at the Mount Sinai Hospital (fig. 3 and 4) and in various instances of mercurial nephropathy.

Once the presence of lower nephron insufficiency has been established, several important differences must be recognized in the management of this disorder in contrast to management of total renal insuf-

15. Walker, A. M.; Hudson, C. L.; Findley, T. H., and Richards, A. N.: Total Molecular Concentration and Chloride Concentration of Fluid from Different Segments of Renal Tubules of Amphibian: Site of Chloride Reabsorption, Am. J. Physiol. **118**:121-129 (Jan.) 1937.

ficiency. It is evident that the normal daily excessive dietary intake of potential acid over base (30 to 80 milliequivalents), unless corrected, tends to perpetuate chronic chloride retention. Moreover, sodium chloride cannot provide enough base to correct this type of acidosis,[15] since its ratio of base to acid (1:1) is lower than that of the circulating blood sodium and chloride (1.4:1). A low chloride intake is consequently as necessary as the feeding of base to overcome hyperchloremic acidosis. This is one of the principal clinical characteristics of pure lower nephron insufficiency (table 3) that distinguish it from the acidosis and renal insufficiency of nephritic uremia.

PURPURA AND HYPERGLOBULINEMIA

The chronic hyperglobulinemia and purpura in this patient were initially thought to be unrelated to each other and to the renal insufficiency. It was noted that the patient of Baines, Barclay and Cooke[15] showed a similar chronic hyperglobulinemia, which was regarded as an attempt to maintain osmotic pressure, or as a sign of dehydration. However, shortly before this paper was submitted for publication Lerner and Watson[16] reported on the presence of a high concentration of a cold-precipitable serum globulin (cryoglobulin) in a patient with chronic purpura and moderately severe glomerular nephritis. These authors also reviewed several cases of "purpura hyperglobulinemia" of varying origin described in the recent Scandinavian literature by Waldenström.[17] Lerner, Barnum and Watson[18] detected excessive amounts of this protein in the serums of a large number of patients with various pathologic conditions. Purpura was postulated to occur when the cold-precipitable globulins were present in such quantities as to increase blood viscosity in the extremities. These authors[16] concluded that "cryoglobulinemia" may be associated with "any one of several etiologic agents, e. g., infection (virus and bacteria), malignancy, hepatic cirrhosis, etc." The occurrence of purpura and hyperglobulinemia in the only 2 described cases of nephrocalcinosis and hyperchloremic acidosis in adults provides ample ground for speculation about the relation of hepatic dysfunction to lower

16. Lerner, A. B., and Watson, C. J.: Studies on Cryoglobulins: I. Unusual Purpura Associated with the Presence of a High Concentration of Cryoglobulin (Cold Precipitable Serum Globulin), Am. J. M. Sc. **214**:410-415 (Oct.) 1947.

17. Waldenström, J.: Incipient Myelomatosis or "Essential" Hyperglobulinemia with Fibrinogenopenia—a New Syndrome? Acta med. Scandinav. **117**:216-247, 1944; "On Terms 'Essential Hyperglobulinemia' and 'Premyeloma'," ibid. **124**:148-159, 1946.

18. Lerner, A. B.; Barnum, C. P., and Watson, C. J.: Studies of Cryoglobulins: II. The Spontaneous Precipitation of Protein from Serum at 5° C in Various Diseases States, Am. J. M. Sc. **214**:416-422 (Oct.) 1947.

nephron nephrosis, but there were no serum cryoglobulins detectable in this case.

ETIOLOGIC FACTORS

It has been well established that sulfanilamide inhibits carbonic anhydrase. This effect may be demonstrated on red blood cells in vitro[12a] or in vivo through the diminution of hydrochloric acid production by the gastric mucosa.[12b] Pitts and Alexander[10] were able to produce blood acidosis and urinary alkalosis in dogs by the administration of sulfanilamide. Similar transient acid-base fluctuations with immediate urinary alkalosis and hyperchloremic acidosis (loss of alkali) were frequently observed in human patients following use of sulfanilamide in therapeutic doses.[19] Pitts and Alexander suggested[10] that the inhibition of carbonic anhydrase results in a temporary impairment of the p_H control mechanism of the distal tubules. With regard to this patient it should be noted that the substituted sulfonamide drugs (such as sulfathiazole and sulfadiazine) did not inhibit carbonic anhydrase to any considerable extent. Nevertheless, hyperchloremic acidosis was reported by Luetscher and Blackman[20] after therapeutic doses of sulfathiazole. Apparently, the sulfathiazole selectively injured the proteins (enzymes) and membrane permeability of the cells involved in p_H adjustment.

Selective injury of the distal tubules by the direct toxic action of various sulfonamide agents was recently demonstrated by both pathologic and physiologic studies. Under conditions of diuresis in rabbits, there is now evidence[21] that acetylated sulfathiazole, as well as free sulfathiazole, is excreted through the tubular cells in large amounts exceeding the amount of drug filtered through the glomeruli. Interference or overloading of this mechanism produced tubular nephrosis without any calculous pelvic or ureteral obstruction.[22] Antopol and associates[23]

19. Roughton and others.[12c] McChesney and others.[13]

20. Luetscher, J. A., Jr., and Blackman, S. S., Jr.: Severe Injury to Kidneys and Brain Following Sulfathiazole Administration: High Serum Sodium and Chloride Levels and Persistent Cerebral Damage, Ann. Int. Med. **18**:741-756 (May) 1943.

21. Becker-Christensen, P., and Per Shou: Experimental Studies on the Excretion of Sulfathiazole by the Kidneys with Normal and Greatly Increased Diuresis (Na_2SO_4), Acta pharmacol. et toxicol. **1**:357-368, 1945.

22. Plummer, N., and McLellan, F.: Production of Sulfapyridine Renal Calculi in Man Following Administration of Sulfapyridine, J.A.M.A. **114**:943-946 (March 16) 1940. Prien, E. L.; Crabtree, E. G., and Frondel, C.: The Mechanism of Urinary Tract Obstruction in Sulfathiazole Therapy: Identification of Crystals in Tissue by Polarized Light, J. Urol. **46**:1020-1032 (Nov.) 1941. Hellwig, C. A., and Reed, H. J.: Fatal Anuria Following Sulfadiazine Therapy, J. A. M. A. **119**:561-563 (June 13) 1942. Long, P. H., and Bliss, E. A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939.

and others[24] were able to reproduce chronic calcifying nephrosis confined to the distal tubules after severe transient sulfonamide toxicity (caused by sulfathiazole and sulfapyridine) in animals. If a massive diuresis was instituted within forty-eight hours of the onset of renal damage, a large proportion of rats[23] survived with minimal signs of systemic disease. Unfortunately, no biochemical studies of the mineral and water metabolism were made on the surviving animals.

In man, the actual clinical recognition of calcification of the distal tubules by roentgenographic examination has not yet been reported to follow sulfonamide therapy. However, extensive pathologic studies were made by Lucké[25] and French[26] on a total of 153 soldiers who died with acute toxic lesions due to various sulfonamide drugs. Many of these patients revealed no clinical evidence of sulfonamide sensitivity prior to death. More than one-half were treated for acute infections, such as nasopharyngitis, pneumonia and meningitis. In a considerable number of these cases the signs of uremia and shock were minimal until just before death. The most characteristic renal lesion observed at autopsy was a lower nephron nephrosis involving the distal portions of the nephron. In some cases French[26] identified acetylated sulfathiazole crystals covered with calcific deposits in and adjacent to the distal tubule cells, and in many cases renal calcification in the distal tubules was an outstanding pathologic feature.

The pathophysiologic picture of lower nephron nephrosis induced with drugs was more clearly delineated by recent studies of Trueta and his associates.[27] They demonstrated the establishment of a "medullary renal circulation" via the vasa recta and subcortical arteriovenous plexuses during various conditions of shock. Dyes injected into animals under these conditions completely by-pass the cortex and are retained

23. Antopol, W.; Lehr, D.; Churg, J., and Sprinz, H.: Changes in the Urinary Tract and Other Organs After Administration of Three Sulfanilamide Derivatives, Arch. Path. **31**:592-602 (May) 1941.

24. Climenko, D. R., and Wright, A. W.: Effect of Continued Administration of Sulfathiazole and Sulfapyridine in Monkeys, Arch. Path. **32**:794-817 (Nov.) 1941. Gross, P.; Cooper, F. P., and Lewis, M.: Urinary Concretions Caused by Sulfapyridine, Proc. Soc. Exper. Biol. & Med. **40**:448-449 (March) 1939.

25. Lucké, B.: Lower Nephron Nephrosis, Mil. Surgeon **99**:371-396 (Nov.) 1946.

26. French, A. J.: Hypersensitivity in the Pathogenesis of the Histopathologic Changes Associated with Sulfonamide Chemotherapy, Am. J. Path. **22**:679-701 (July) 1946.

27. Trueta, J.; Barclay, A. D.; Franklin, K. L.; Daniel, P., and Pritchard, M. M. L.: Renal Pathology in the Light of Recent Neurovascular Studies: Preliminary Communication, Lancet **2**:237-238 (Aug. 17) 1946.

in the medulla. The diversion of blood flow is in effect an arteriovenous shunt produced in an attempt to conserve body fluid. These workers showed that the diversion of blood flow is actually mediated by stimulation of the renal nerves during states of stress (pneumonia, hemorrhage, shock, hysteria and drug intoxication). According to Trueta and associates, it is probable that "sulfa kidney" represents a defense mechanism by which the renal cortex is excluded from circulating toxins or other agents.

TABLE 4.—*Etiologic Classification of Diffuse Renal Calcifications*

A. Primary Urinary Tract Disease
   1. Chronic renal insufficiency (glomerular nephritis, renal hypogenesis, obstructive renal disease)
   2. Pyelonephritis (Hemophilus influenzae)
   3. Polycystic kidneys
   4. Tuberculous renal disease
   5. Echinococcosis of kidneys
   6. Tubular dysfunction, congenital
      (*a*) Idiopathic nephrocalcinosis with hyperchloremia, acidosis, rickets and dwarfism
      (*b*) DeToni-Fanconi syndrome (no calcification)

B. Metabolic Disturbances
   1. Primary hyperparathyroidism
   2. Acute or chronic hypochloremic alkalosis (pyloric obstruction, vomiting, tetany)
   3. Chronic acidosis (ammonium chloride, sodium phosphate)
   4. Hypervitaminosis D
   5. Diabetes insipidus

C. Toxic Nephropathy
   1. Mercurial (terminal and straight portion of proximal convoluted tubule)
   2. Uranial nitrate (straight portion of proximal convoluted tubule)
   3. Sulfonamide drugs (distal portion, convoluted tubule and collecting tubule)
   4. Oxalate, ethylene glycol (proximal portion of convoluted tubule)
   5. Potassium dichromate (first portion of proximal convoluted tubule)
   6. Safranin O
   7. Carbon tetrachloride

D. Blockage Nephropathy
   1. Massive calcium mobilization (bone carcinoma, multiple myeloma)
   2. Hemoglobin, myoglobin
   3. Sulfonamide drugs

Thus, the evidence points to the possibility that sulfathiazole and other sulfonamide drugs may occasionally result in transient, unrecognized renal toxicity in patients with complicating infection or trauma. A chronic nephrocalcinosis may follow in association with the clinical syndrome of a pure lower nephron insufficiency. In the absence of any other etiologic factors, it has seemed warranted to adopt this explanation of the pathogenesis of the lesion in this patient.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis of nephrocalcinosis with hyperchloremic acidosis one must consider a multiplicity of etiologic agents and physiologic conditions favoring the development of dystrophic renal calcification.

Any case in which renal calcification appears to be principally in the medulla may present itself with the syndrome of lower nephron insufficiency. However, most renal calcifications are observed to be either local or spotty or, occasionally, distributed diffusely in both the cortices and the medullas. Since it is impossible to discuss fully the differential diagnosis here, a synoptic table of the numerous etiologic factors which may produce lesions resembling nephrocalcinosis is presented.

Certain abnormal physiologic states may also produce nephrocalcinosis. These are usually characterized by acidosis, alkalosis, or elevations in the serum calcium or phosphorus content. A congenital basis for nephrocalcinosis with hyperchloremic acidosis was even suggested[1d] by analogy to the deToni-Fanconi syndrome, a congenital primary noncalcifying disorder of the proximal tubules. However, it is noteworthy that Albright and associates[1a] were unable to describe any definite cause for their case of "idiopathic nephrocalcinosis" and were unable to state whether the calcification was primary or secondary in origin. Hyperchloremic acidosis produced by noncalcifying disease of the distal tubules was described even in cases of sulfonamide toxicity in adults,[20] in congenital chronic pyelonephritis in infants[4] and in diabetes insipidus.[5] It seems reasonable to assume that hyperchloremic acidosis may occur secondarily to many etiologic agents which to a greater or lesser extent confine their effects to the distal tubules. Calcium deposition appears to be a usual but not necessary sequel to damage or interference in the mechanism for p_H in the lower nephrons.

NOTE.—Since this manuscript was prepared, Albright[28] and his coworkers have published an extensive discussion of the alterations in homeostatic mechanisms which are associated with clinical conditions manifested by osteomalacia (adult rickets). One new case of hyperchloremic acidosis and nephrocalcinosis was presented. The patient was 18 years old with nine years of known symptoms.

SUMMARY

The syndrome of distal tubule nephrocalcinosis with chronic hyperchloremic acidosis is described in man. This renal lesion was associated with an unusual form of chronic discrete lower nephron insufficiency

28. Albright, F. A.; Burnett, C. H.; Parson, W.; Reifenstein, E. C., Jr., and Roos, A: Osteomalacia and Late Rickets, Medicine **25**:399-479 (Dec.) 1946.

manifested by isosthenuria, diminished ammonia excretion and fixed urinary alkalosis in the presence of a blood acidosis, hyperchloremia and relatively good glomerular function. A patient with this syndrome was successfully treated for almost three years with a regimen employing sodium citrate and citric acid. A brief discussion of the physiologic mechanism of lower nephron insufficiency is included, as well as a synopsis of the differential diagnosis in the presence of this lesion. The role of sulfathiazole as a possible etiologic factor in the production of nephrocalcinosis is discussed. The association of purpura and hyperglobulinemia as a manifestation of atypical hepatic dysfunction is mentioned in relation to the lower nephron nephrosis.

EXTRACELLULAR FLUID IN CARDIAC EDEMA AND ASCITES

LOUIS R. FERRARO, M.D.
MAX M. FRIEDMAN, Ph.D.*
AND
HENRY E. MORELLI, M.D.
BRONX, N. Y.

THE IMPORTANCE of determining quantitatively the amount of extracellular fluid deposited as edema or ascites in pathologic states is well appreciated. Previous laboratory methods for this determination were open to criticisms and objections. Experimental work showed that the chloride ion is confined principally to the extracellular area.[1] In 1939, Wallace and Brodie[2] compared the $\frac{\text{tissue Br}}{\text{serum Br}}$ to $\frac{\text{tissue Cl}}{\text{serum Cl}}$ and concluded that the ratio of distribution of these ions is similar in all tissues of the body with the exception of the brain. Later, Brodie, Brand and Leshin[3] proposed a quantitative test for extracellular fluid by injection of sodium bromide intravenously and determination of its level in the serum and urine. Bromide was selected for this purpose since it is nontoxic in the doses administered, rapidly distributed throughout the body, slowly excreted and capable of accurate analysis. It is also dispersed between serum and transudates according to the Gibbs-Donnan equilibrium.

In a preliminary report, Brodie, Friedman and Ferraro,[4] utilizing the bromide method, presented figures for the volume of extracellular fluid of normal persons computed on the basis of surface area. In men the

From the Pathological Laboratories at Fordham Hospital.

1. Harrison, H. E.; Darrow, D. C., and Yannet, H.: The Total Electrolyte Content of Animals and Its Probable Relation to the Distribution of Body Water, J. Biol. Chem. **113**:515, 1936. Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., Charles C Thomas, Publisher, 1935. Manery, J. F., and Hastings, A. B.: Distribution of Electrolytes in Mammalian Tissues, J. Biol. Chem. **127**:657, 1939.

2. Wallace, G. B., and Brodie, B. B.: Distribution of Administered Bromide in Comparison with Chloride and Its Relation to Body Fluids, J. Pharmacol. & Exper. Therap. **65**:220, 1939.

3. Brodie, B. B.; Brand, E., and Leshin, S.: The Use of Bromide as a Measure of Extracellular Fluid, J. Biol. Chem. **130**:555, 1939.

4. Brodie, B. B.; Friedman, M. M., and Ferraro, L. R.: Studies on Extracellular Fluid, J. Biol. Chem. **140**:xxi, 1941.

volume was observed to range from 10 to 11 liters per square meter and in women from 9 to 10 liters.

This study was conducted for the purpose of determining the volume of extracellular fluid in pathologic states and observing its fluctuations during therapeutic regimens. Patients were selected from the medical wards of Fordham Hospital.

METHOD OF STUDY

The patient was not required to restrict either food or fluid during the test period. Obviously, bromide or iodide therapy were contraindicated during this time, and, likewise, diuretics were withheld. Since bromide is normally present in the serum in small amounts, it is essential to determine its level prior to the test.

The procedure was as follows:

1. Twenty cubic centimeters of blood was withdrawn by venipuncture and placed under a layer of liquid petroleum U.S.P. in a test tube.

2. A known amount of sterile 10 per cent sodium bromide solution (usually 25 to 50 cc.) was slowly injected. The time was carefully noted and the collection of a twenty-four hour specimen of urine was begun.

3. At the end of twenty-four hours, a second specimen of blood was withdrawn in the same manner as before.

4. The blood was allowed to clot. The test tubes were centrifuged at a moderate speed for twenty minutes and the serum removed.

The specimens of both serum and urine were then analyzed for bromide by the method of Brodie and Friedman.[5] In brief, this consisted of an alkali ashing with sodium hydroxide, followed by the addition of solid potassium nitrate to the resulting melt so as to complete the oxidation. Thus, the organic matter was completely destroyed with no loss of bromide. The bromide was then oxidized to bromate by sodium hypochlorite solution, the excess hypochlorite reduced with sodium formate, and the bromate estimated iodometrically.[6]

CALCULATIONS

The calculations for volume of extracellular fluid were made according to the formula of Hastings and Eichelberger:[7]

$$\text{Total extracellular fluid (liters)} = \frac{\text{Amount Br (mg.) remaining in body} \times 0.88}{\text{Br (mg.) per liter of serum}}$$

The amount of bromide remaining in the body is determined by subtracting the amount of bromide excreted in the urine in twenty-four

5. Brodie, B. B., and Friedman, M. M.: The Determination of Bromide in Tissues and Biological Fluids, J. Biol. Chem. **124**:2, 1939.

6. This method was subsequently simplified by one of us (Friedman, M. M.: J. Biol. Chem. **144**:519, 1942). A trichloroacetic filtrate was substituted for the entire ashing procedure, thereby saving considerable time with no sacrifice in accuracy.

7. Hastings, A. B., and Eichelberger, L.: The Exchange of Salt and Water Between Muscle and Blood, J. Biol. Chem. **117**:73, 1937.

hours from the amount of bromide (in milligrams) administered intravenously. The denominator is obtained by subtraction of the amount of bromide demonstrated in the pretest serum from that determined in the serum twenty-four hours after the injection. The correction factor 0.88 takes into account the effect of the serum protein and the Gibbs-Donnan equilibrium. Loss of bromide in the feces and perspiration is disregarded since it is negligible within the first twenty-four hours. The total excretion of bromide during the test period was in every instance less than 3 per cent of the total injected, usually less than 1 per cent.

TABLE 1.—*Results of Simultaneous Determinations of Bromide in Serum and Ascitic Fluid*

Case No.	Serum Bromide, Mg./L.	Bromide in Ascitic Fluid, Mg./L.
1	109	118
2	65	68
3	100	108
4	65.5	67
5	126	134

The surface area is computed by the DuBois formula:

$$(\text{Weight})^{0.425} \times (\text{Height})^{0.725} \times 71.84 = \text{Surface area in square centimeters}$$

with the weight and height given in kilograms and centimeters, respectively. Nomograms for direct readings of surface area are readily available.

Prior to the systematic study of patients, it was deemed advisable to ascertain the relative distribution of bromide between serum and ascitic fluid in patients with ascites. Five such patients were selected at random and the bromide test performed according to the technic described. Serum and ascitic fluid were then removed simultaneously and bromide determinations made, with the results shown in table 1. The slightly higher values obtained for the ascitic fluid were essentially due to the effect of the Gibbs-Donnan equilibrium and to the lower concentration of protein.

ANALYSIS OF CASES

A. Cardiac Disease.—The first series consisted of 12 patients with cardiac disease admitted to the hospital in acute distress with signs and symptoms of cardiac failure and demonstrable edema. For each of the first 6 patients, a single bromide test was performed, while for the remainder 2 distinct and separate tests were done after various intervals of time (table 2).

It is evident that all these patients revealed an excess volume of extracellular fluid which varied during the acute stage from 6.8 to 31.2 liters above the normal. Therapy consisted of rest in bed, adequate administration of digitalis and diuretics and restricted fluid intake. Four patients (cases 8, 9, 10 and 11) were discharged "greatly improved" as far as could be determined by clinical means, yet bromide tests performed just prior to discharge showed an excess of extracellular fluid, which ranged from 2.9 to 7.6 liters. In 1941, Seymour and associates[8] in a study of 6 patients with cardiac disease stated that "the mean value

TABLE 2.—*Results of Determinations of Bromide in the Patients With Cardiac Diseases*

Case No.	Age, Yr.	Sex	Diagnosis	Date of Determinations	Extracellular Fluid, L. Sq. M.	Total Extracellular Fluid, L.	Normal Extracellular Fluid, L.	Excess Extracellular Fluid, L.
1	59	F	Auricular fibrillation		24.3	52.3	21.1	31.2
2	64	M	Syphilitic heart disease		15.9	28.7	18.1	10.6
3	65	F	Hypertensive heart disease		16.9	31.8	18.2	13.6
4	73	F	Arteriosclerotic heart disease		20.0	31.4	15.7	15.7
5	78	M	Hypertensive heart disease		17.9	29.6	16.5	13.1
6	36	F	Chronic rheumatic heart disease		15.4	19.4	12.6	6.8
7	63	F	Hypertensive heart disease	5/10 7/17	15.9 13.8	26.7 22.4	16.8 16.6	9.9 5.8
8	60	M	Rheumatic heart disease(?)	7/14 7/30	17.8 13.4	30.9 22.8	17.4 17.0	13.5 5.8
9	51	M	Hypertensive heart disease	7/14 7/31	14.6 11.8	25.4 19.8	16.5 16.8	8.9 3.0
10	67	M	Hypertensive heart disease	9/12 9/29	20.8 11.7	36.0 19.5	17.5 16.6	18.5 2.9
11	57	F	Hypertensive heart disease	7/24 9/29	20.7 15.3	34.0 21.9	16.5 14.3	17.5 7.6
12	53	M	Auricular fibrillation	5/11 5/24	14.5 15.3	27.9 29.5	19.2 19.3	8.7 10.2

of total extracellular fluid in the recovery phase was 32 per cent of total body weight—still almost 50 per cent above normal." In our study, the values for extracellular fluid at the time of clinical recovery also averaged about 32 per cent of body weight. However, when computed on the basis of surface area, this volume amounted to about 20 per cent above normal. The discrepancy is explained by our previous observation[4] that calculations based on body weight in normal persons result in wide variations as compared with those computed on the basis of surface area.

8. Seymour, O. B.; Pritchard, W. H.; Longley, L. P., and Hyman, J. M., Jr.: Cardiac Output, Blood and Interstitial Fluid Volumes, Total Circulating Serum Protein, and Kidney Function During Cardiac Failure and After Improvement, J. Clin. Investigation **21**:229, 1942.

B. Cirrhosis of Liver.—Determinations of volume of extracellular fluid were performed on 5 patients with ascites due to cirrhosis of the liver. The results are listed in table 3. These patients were all treated with mercurial diuretics, rest in bed and dietary regimen. Paracenteses were performed on 2 of the patients. The greatest accumulation of extracellular fluid was in the first patient (case 1), with a total volume of 44.2 liters, 25.3 liters in excess of normal. The fluid balance of none of these patients was restored to normal in spite of intensive and prolonged therapy. In the first and second patients (cases 1 and 2), paracenteses were of temporary value and were followed by greater accumulation of fluid than had previously existed.

TABLE 3.—*Results of Determinations of Bromide in Patients With Ascites*

Case No.	Age, Yr.	Sex	Date of Determinations	Extracellular Fluid, L./Sq. M.	Total Extracellular Fluid, L.	Normal Extracellular Fluid, L.	Excess Extracellular Fluid, L.
1	58	M	1/6	20.8	38.9	18.7	20.2
			1/13	18.2	33.3	18.3	15.0
			2/4	23.4	44.2	18.9	25.3
			7/14	20.7	38.0	18.5	19.5
			7/28	22.6	42.4	18.8	23.6
2	61	M	1/2	17.2	33.3	19.6	13.7
			1/6	16.6	32.1	19.4	12.7
			1/24	22.1	44.2	20.0	24.2
3	53	M	3/24	18.2	31.9	17.5	14.4
			3/29	17.8	30.9	17.3	13.6
			4/1	17.8	30.9	17.3	13.6
4	74	M	1/28	17.3	26.0	15.0	11.0
			7/17	20.9	30.9	14.8	16.1
5	31	M	1/27	16.7	36.7	22.0	14.7

COMMENT

Extracellular fluid is composed of blood plasma, which constitutes about 5 per cent of the body weight, and interstitial fluid, comprising about 15 per cent of body weight. Since bromide, as well as chloride, enters blood cells and gastrointestinal secretions, it is not possible to obtain the absolute value of extracellular fluid by the technic described. However, this loss of the bromide ion is minimal, so that close approximations to the ideal are obtained and valid observations may be made.

The intravenous administration of sodium bromide in a normal person results in complete diffusion of this halide throughout the extracellular compartment within a period of two hours. However, in edematous or ascitic patients, much longer time is required for diffusion and equilibrium to occur. Therefore, in these conditions, the blood sample for analysis should be collected twenty-four hours after the injection of the bromide.

The clinical evaluation of the amount of extracellular fluid in edematous or ascitic states is crude and at times misleading. Wiggers

stated that a 10 per cent increase in the fluid content of tissues is a prerequisite to its pitting. Gottlieb reported that as much as 6,000 cc. of edema fluid may be present in the body without demonstrable evidence of edema. For these reasons, we felt the need of a reliable and relatively simple test for the accurate determination of extracellular fluid. Such a determination permits one (1) to establish the level of extracellular fluid at the time the patient is first examined; (2) to follow the fluctuations of this fluid during therapy; (3) to ascertain the presence of excess accumulation of fluid in the absence of positive clinical findings, and (4) to determine the time at which the patient is restored to a normal level for extracellular fluid. It is interesting to note that none of the patients with cardiac disease in this group showed a return to a normal fluid level. However, further studies are required to determine whether normal limits of extracellular fluid are regained by patients who have had episodes of cardiac failure.

SUMMARY

1. The volume of extracellular fluid was determined by the bromide method in two types of conditions, namely, edema due to cardiac disease and ascites resulting from cirrhosis of the liver.

2. Fluctuations in the volume of extracellular fluid were noted during therapeutic regimen by repeated bromide tests.

3. Bromide tests performed on 5 cardiac patients at the time of clinical recovery revealed an excess of extracellular fluid which varied from 2.9 to 7.6 liters above the normal. These patients had no demonstrable edema or signs of cardiac failure, at that time.

4. Sodium bromide produced no ill effects in the doses administered.

Fordham Hospital, New York 58 (Dr. Ferraro and Dr. Morelli). Queens General Hospital, Jamaica, N. Y. (Dr. Friedman).

HEPATIC FUNCTION DURING THE HYPOPROTEINEMIA OF RENAL DISEASE

ROBERT I. BOYD, M.D.
PASADENA

THERE is general agreement that the liver is involved in the formation of plasma proteins. The evidence is well defined in the case of fibrinogen[1] and of prothrombin,[2] but in the case of other globulin fractions serious question remains. The work of Whipple and his collaborators[3] relates the liver to hypoalbuminemia under the conditions of their experiments. Furthermore, in the later stages of cirrhosis of the liver it has long been known that the serum albumin concentration is less than normal.[4]

A similar and often even more pronounced decrease in serum albumin concentration is seen in patients in the degenerative stage of glomerular nephritis with edema. It is not immediately apparent why this plasma anomaly should occur as a direct consequence of the renal lesion. There is agreement that mere loss of protein in the urine cannot be regarded as

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From the Department of Medicine, Stanford University School of Medicine, San Francisco.

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3. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production, and Utilization, Physiol. Rev. **20**:194-217, 1940. Whipple, G. H.: Robscheit-Robbins, F. S., and Hawkins, W. B.: Eck Fistula Liver, Subnormal in Producing Hemoglobin and Plasma Proteins on Diets Rich in Liver and Iron, J. Exper. Med. **81**:171-191, 1945. Whipple, G. H.: Hemoglobin, Plasma Protein, and Cell Protein: Their Production and Interchange, Springfield, Ill., Charles C Thomas, Publisher, 1948.

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an adequate explanation for the decrease in the concentration of albumin in the plasma,[5] nor can the concentration in the plasma be raised by increasing the amount of protein ingested.[6] It therefore seems reasonable to consider the possibility that in these edematous patients the functional capacity of the liver to maintain plasma albumin may be defective. If that supposition were correct, it might be anticipated that one should find evidence of a defect in other hepatic functions. Elman and Heifetz[7] found functional and anatomic evidence of hepatic impairment in dogs in which hypoalbuminemia was produced by a protein-deficient diet.

We have therefore carried out a systematic investigation of hepatic function in 71 patients with diffuse bilateral renal diseases, using procedures available to the clinician. The limitations of studying hepatic function by clinical measures are apparent, but they may be diminished in part by employing simultaneously a variety of procedures.[8]

A group of tests was chosen which are sensitive to changes in hepatocellular functions. Observations used were measurement of the serum bilirubin, directly reacting and total, the cephalin-cholesterol flocculation test, the thymol turbidity test and thymol flocculation. In some instances the urinary urobilinogen was measured.[9]

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5. Melnick, D., and Cowgill, G. R.: The Problem of Hypoproteinemia, Yale J. Biol. & Med. **10**:49-62, 1937; The Influence of Prolonged Intensive Plasmapheresis upon Ability of Organism to Regenerate Serum Protein, J. Exper. Med. **66**:493-504, 1937. Bloomfield, A. L.: Effect of Restriction of Protein Intake on Serum Protein Concentration of the Rat, ibid. **57**:705-720, 1933. Barnett, C. W.; Jones, R. B., and Cohn, R. B.: Maintenance of Normal Plasma Protein Concentration in Spite of Repeated Protein Loss by Bleeding, ibid. **55**:683-693, 1932.

6. Persike, E. C., and Addis, T.: Food Protein Consumption in Glomerular Nephritis: Effect on Proteinuria and the Concentration of Serum Protein, Arch. Int. Med. **81**:612-622 (May) 1948.

7. Elman, R., and Heifetz, C. J.: Experimental Hypoalbuminemia: Its Effect on Morphology, Function, and Protein and Water Content of the Liver, J. Exper. Med. **73**:417-430, 1941.

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9. Measurements of sulfobromophthalein retention with dosage of 5 mg. per kilogram and determinations of blood levels at forty-five and sixty minutes in 2 edematous patients were made. The results were normal. Inasmuch as some of the dye is excreted in the urine and the effects of renal disease on the test have not been studied, these tests were not used further.

These observations were made on 71 patients who were being treated in the Clinic for Renal Disease of the Stanford University School of Medicine. Control groups of 10 healthy adults, whose responses to the tests were all within normal limits, and 2 patients with hepatic disease, whose responses were abnormal in each instance, also were tested.

METHODS

The cephalin-cholesterol flocculation test was performed according to the directions of Hanger,[10] with the use of the Wilson brand cephalin-cholesterol mixture. Results reading plus-minus at twenty-four hours and 1 plus at forty-eight hours were regarded as the upper limit of normal.[8]

The thymol turbidity test of Maclagan[11] was modified to p_H 7.55.[8a] The hydrogen ion concentration was measured galvanometrically. Results were read at thirty minutes and expressed in terms of the Kingsbury turbidity standards.[12] Neefe's maximum normal of 3 units was used.[13] The thymol flocculation test was read at twenty-four hours, and any perceptible flocculation regarded as abnormal.[13]

The serum bilirubin, direct and total, was measured by the method of Malloy and Evelyn[14] on an Evelyn colorimeter. The direct reaction was read at thirty minutes. Normal limits were taken to be 1.0 mg. per hundred cubic centimeters for the total serum bilirubin.[15] The normal limit for the thirty minute reading of "direct" bilirubin is less well established than that for readings at one minute, and it would have been preferable to use the latter.[15] In Watson's series of normal persons in whom measurements were made at fifteen minutes, 0.35 mg. is well within the maximal range,[15] and we have used that figure as a normal limit. In some cases the direct bilirubin was not measured quantitatively if a negative qualitative result was obtained. Total bilirubin was measured in each instance.

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13. Neefe, J. R.: Results of Hepatic Tests in Chronic Hepatitis Without Jaundice: Correlation with Clinical Course and Liver Biopsy Findings, Gastroenterology **7**:1-19, 1946.

14. Malloy, H. T., and Evelyn, K. O.: Determination of Bilirubin with Photoelectric Colorimeter, J. Biol. Chem. **119**:481, 1937.

15. Watson, C. J.: Some Newer Concepts of the Natural Derivatives of Hemoglobin, Blood **1**:99-120, 1946.

Urinary urobilinogen was measured with an Evelyn colorimeter by the short method of Watson.[16]

MATERIAL

I. Fifty-two patients with glomerular nephritis were studied. The diagnosis was well founded for each, and on each of them consecutive observations were made of the hematocrit value, the serum protein and creatinine concentrations, the daily rate of protein excretion in the urine, the urinary sediments, qualitative and quantitative, as well as physical examinations and whatever special studies were indicated, extending over a space of time varying from several weeks to twenty years. The classification of these patients into subgroups followed well defined criteria[17] in most cases but had to be arbitrary in a few of them. The serum protein concentration and the presence or absence of edema were important for this study, and emphasis was put on them in segregating the cases into the following categories.

Twenty-four patients were observed in the degenerative stage of glomerular nephritis, with edema. Their range of serum protein concentrations was from 2.8 to 5.0 Gm. per hundred cubic centimeters and of creatinine from 0.7 to 9.25 mg.

Twenty-one were observed in the latent stage. In this classification were placed a variety of patients, with renal lesions ranging from those that were minimal and healing to those that were extensive and progressive, the patients with the latter being separated from those in the degenerative stage only by the absence of edema. In some of these an increasing proteinuria, changing urinary sediments, and decreasing serum protein concentrations attested to the approach of frank edema. The serum protein concentrations varied from 5.4 to 6.5 Gm. per hundred cubic centimeters. A few of the patients had retention of creatinine, the highest concentration being 3.1 mg. per hundred cubic centimeters.

Three patients were in the terminal stage of glomerular nephritis, with uremia and hypertension. Their serum protein concentrations varied from 5.0 to 5.6 Gm. per hundred cubic centimeters. Before reaching this impasse they had been seen in the clinic during the degenerative

16. Watson, C. J.; Schwartz, S.; Sborov, V., and Bertie, E.: A Simple Method for Quantitative Recording of the Ehrlich Reaction as Carried out with Urine and Feces, Am. J. Clin. Path. **14**:605-615, 1944. Schwartz, S.; Sborov, V., and Watson, C. J.: The Quantitative Determination of Urobilinogen by Means of the Evelyn Photoelectric Colorimeter, ibid. **14**:598-604, 1944. Kelly, W. D.; Lewis, J. N., and Davidson, C. S.: The Determination of Urine Urobilinogen: The Interpretation of Rate of Color Development of the Ehrlich Reaction, J. Lab. & Clin. Med. **31**:1045-1049, 1946.

17. Addis, T.: Glomerular Nephritis, New York, The Macmillan Company, 1948.

stage when they were edematous, their serum protein concentrations low, and their daily rate of protein excretion in the urine high. Each of them died within six months after the studies of hepatic function were made, 1 of them within a week.

Two were seen in the initial phase of the disease, and 2 others were classified as healed, having been observed for several years. Each of the latter had been edematous for a long period before the edema disappeared, and, finally, the evidences of a renal lesion gradually disappeared.

II. Sixteen patients with renal diseases other than glomerular nephritis comprised this group. They were without edema but had proteinuria. Their diagnoses included essential hypertension with nephrosclerosis, pyelonephritis, congenital bilateral renal hypoplasia, polycystic disease, focal glomerulitis after hemolytic streptococcic bacteremia, nephrolithiasis, and disseminated lupus.[18]

III. Four patients of this series had a disease marked by edema, considerable proteinuria, low serum protein concentrations ranging from 2.9 to 5.0 Gm. per hundred cubic centimeters, and normal serum creatinine concentrations. They did not have glomerular nephritis, but belonged to a group whose disease has been regarded as possibly arising from abnormality in the formation of plasma proteins.[19]

RESULTS

The results are shown in the table. These figures clearly show that we have failed to find evidence of impaired hepatic function in 71 patients with renal disease, even in those in whom there was edema and pronounced decrease in serum protein concentration.

There was complete normality of response to each of the procedures used, save in 1 patient with glomerular nephritis in the degenerative stage in whom the thymol turbidity measured 4 units.[20] The other tests on this patient gave normal results.

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18. As was consistent with her disease, the patient with disseminated lupus had strongly positive reactions to cephalin-cholesterol and thymol flocculation tests, a positive reaction to the thymol turbidity test, and a normal serum bilirubin content. The data on this patient were excluded from the table.

19. Addis, T.: Renal Degenerations Due to Protein Reabsorption by the Kidney, Stanford M. Bull. 3:67-71, 1945. Addis.[17]

20. Maclagan[11] described 5 units as normal for the thymol turbidity test, but the 3 unit maximum of Neefe[13] was used herein.

Diagnosis	Number of Cases	Serum Bilirubin Mg./100 Cc. Direct Average	Direct Maximum	Total Average	Total Maximum	Cephalin-Cholesterol Flocculation Maximum 24 Hour Reading	Cephalin-Cholesterol Flocculation Maximum 48 Hour Reading	Thymol Turbidity, Kingsbury Units Average	Thymol Turbidity, Kingsbury Units Maximum	Thymol Flocculation Maximum	Urine Urobilinogen, Ehrlich Units per Hour Minimum	Urine Urobilinogen, Ehrlich Units per Hour Maximum
I. Glomerular nephritis												
(a) degenerative	24	0.028	0.1	0.30	0.7	0	(±)	0.55	4*	0	0.05	0.71
(b) latent	21	0.066	0.1	0.48	0.9†	0	(+)	0.25	3	0‡	0.00	0.03
(c) terminal	3	0.07	0.1	0.31	0.4	0	0	0.	0	0		
(d) initial	2	0	0	0.26	0.3	0	0	0.	0	0		
(e) healed	2	Not measured				0	0	0.	0	0		
II. Other renal diseases (see text)	15	0.14	0.30	0.32	0.7†	0	0	0.3	2	0		
III. Patients with proteinuria and edema (see text)	4	0.11	0.2	0.39	0.6	0	0	0.03	1	0		

†This excludes 1 patient recently ill with infectious hepatitis whose serum had been mildly icteric since. Total serum bilirubin contents were 1.15 and 1.45 mg. respectively. All other tests gave normal results.

*In only one specimen of serum was the value above the normal 3 units. (see text).

‡This excludes 1 patient with active duodenal ulcer, visualized, whose thymol flocculation was 2 plus. All other tests in this patient gave normal results.

COMMENT

Many details are not clear about the process of maintaining the concentration of proteins in the plasma; nor has it been finally determined which organs are chiefly concerned in this process. The data here presented suggest, but do not prove, normalcy of hepatic function during alterations of the serum proteins which are qualitative[21] as well as quantitative.[22] That suggestion is countenanced by certain findings of others. Several patients have been observed to have hypoproteinemia without demonstrable cause and without proteinuria.[23] Hepatic function has been studied in detail in a few such persons and has been found normal. The proposal has been made that the involved site of protein regulation is elsewhere.[23] The observation of Kunkel and Ward[24] that in glomerular nephritis the liver is capable of normal or hypernormal formation of plasma esterase, whereas in hepatic disease this capacity is impaired, provides further evidence pointing toward normal function of the liver during the hypoalbuminemia which occurs in renal disease.

SUMMARY

Fifty-two patients with glomerular nephritis in various stages and 21 patients with other diffuse renal diseases were studied by means of a group of tests of hepatic function. Evidence of impaired hepatic function was not found, either in the edematous patients with lowered serum protein concentrations or in the nonedematous ones.

960 East Green Street, Pasadena 1.

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23. Rytand, D. A.: Edema with Unexplained Hypoproteinemia: A Syndrome of Defective Formation of Serum Proteins in the Absence of "Loss and Lack" of Protein and Demonstrable Hepatic Disease, Arch. Int. Med. **69**:251-262 (Feb.) 1942.

24. Kunkel, H. G., and Ward, S. M.: Plasma Esterase Activity in Patients with Liver Disease and the Nephrotic Syndrome, J. Exper. Med. **86**:325-337, 1947.

EPIDEMIC PLEURODYNIA: CLINICAL AND ETIOLOGIC STUDIES BASED ON ONE HUNDRED AND FOURTEEN CASES

JOHN J. FINN JR., M.D.
AND
THOMAS H. WELLER, M.D.
BOSTON
AND
HERBERT R. MORGAN, M.D.
ANN ARBOR, MICH.

DURING the late summer and early fall of 1947, an epidemic acute febrile illness characterized by headache, pyrexia and paroxysmal pain in the region of the diaphragm occurred in Massachusetts. Clinically it closely resembled a malady first described in Iceland by Finsen[1] in 1856, who called it "pleurodynia." The same syndrome has since been variously designated as "Bornholm disease," "epidemic muscular rheumatism," "acute benign dry pleurisy," "epidemic pleuritic pain," "Bamle disease" and "devil's grip." The last name was based on the description of the pain in the chest experienced by one of Dabney's[2] patients in the first outbreak reported from the United States. The literature on the disease was reviewed by Sylvest[3] in 1934 and has been brought up to date by Scadding.[4]

Dr. Morgan is Senior Fellow in the Medical Sciences, National Research Council.

From the First and Third (Tufts) Medical Services, the Thorndike Memorial Laboratory, and the Second and Fourth (Harvard) Medical Services, Boston City Hospital; the Research Division of Infectious Diseases, the Children's Medical Center; the department of medicine, Tufts College Medical School, and the department of pediatrics and medicine, Harvard Medical School, Boston.

1. Finsen, J.: Iagtagelser angaaende sygdomsforholdene i Island, Copenhagen, 1874; Cited in Epidemic Myalgia, or Pleurodynia, editorial, J.A.M.A. **102**:460-461 (Feb. 10) 1934.

2. Dabney, W. C.: An Account of an Epidemic Resembling Dengue, Which Occurred in and Around Charlottesville and the University of Virginia in June, 1888, Am. J. M. Sc. **96**:488-494, 1888.

3. Sylvest, E.: Epidemic Myalgia: Bornholm Disease, translated by H. Andersen, London, Oxford University Press, 1934.

4. Scadding, J. G.: Acute Benign Dry Pleurisy in the Middle East, Lancet **1**:763-766, 1946.

The etiology remains obscure. Small[5] found inclusion bodies in the erythrocytes in 2 cases, which induced him and Torrey[6] to believe that the disease was caused by a plasmodium. Other workers have not confirmed these observations. Crone and Chapman[7] failed to induce the disease in a human volunteer by the injection of whole blood obtained from a patient on the fourth day of "epidemic pleurodynia." Bacteriologic studies have given uniformly negative results, although Cooper and Keller[8] and MacDonald and associates,[9] studying the Cincinnati epidemic in 1935, noted the constant presence of an alpha hemolytic streptococcus in cultures from throat swabs and nasal washings. However, they were unsucessful in attempts to transmit the disease to animals by inoculation of cultures of this organism or by means of nasal washings. They also considered the possibility of a common etiologic relationship between pleurodynia and a concurrent outbreak of benign lymphocytic meningitis. Attempts by Henle[10] to isolate a causal organism by the injection of nasal washings, blood, cerebrospinal fluid and urine from patients of the Philadelphia epidemic of 1943 into hamsters, mice, guinea pigs, rabbits and chick embryos were unsuccessful, and complement fixation tests for antibodies to the viruses of influenza and lymphocytic choriomeningitis gave negative results. Habel,[11] using material obtained from patients of the Brooklyn epidemic,[12] produced fever and leukopenia in monkeys but was unable to maintain in serial passages in monkeys the agent responsible for these symptoms.

In this paper the clinical aspects of 114 cases of epidemic pleurodynia observed at the Boston City Hospital in 1947 are summarized. A review of the procedures that were followed in an attempt to isolate an etiologic

5. Small, J. C.: A Protozoan Organism Within the Erythrocytes of Patients Suffering from Epidemic Pleurodynia ("Devil's Grip"), Am. J. M. Sc. **168**:570-573, 1924.

6. Torrey, R. G.: Epidemic Diaphragmatic Pleurodynia or "Devil's Grip," Am. J. M. Sc. **168**:564-570, 1924.

7. Crone, N. L., and Chapman, E. M.: Epidemic Pleurodynia, New England J. Med. **209**:1007-1008, 1933.

8. Cooper, M. L., and Keller, H. M.: Bacteriologic Studies of an Epidemic of Pleurodynia, Am. J. Dis. Child. **54**:231-239 (Aug.) 1937.

9. MacDonald, R. R.; Hewell, B., and Cooper, M. L.: Epidemic Myalgia or Pleurodynia: Clinical and Bacteriologic Studies, Am. J. Dis. Child. **53**:1425-1434 (June) 1937.

10. McConnell, J.: An Epidemic of Pleurodynia with Prominent Neurologic Symptoms and No Demonstrable Cause, Am. J. M. Sc. **209**:41-48, 1945.

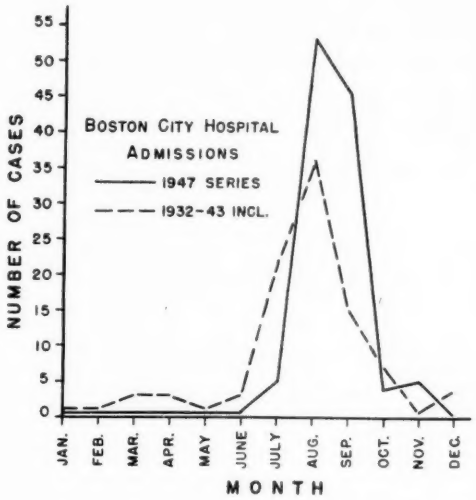
11. Habel, K.: Personal communication to the authors.

12. Howard, T.; Weymuller, C. A.; Edson, J.; Ittner, E.; Watson, J., and Cassidy, M. L.: Epidemic Pleurodynia in Brooklyn in the Summer of 1942, J.A.M.A. **121**:925-929 (March 20) 1943.

agent is also presented. A preliminary report of this epidemic has been published elsewhere.[13]

INCIDENCE AND DISTRIBUTION

The first patient was admitted to the hospital during the last week in July. During the second week in August the number of patients admitted with the disease reached a maximum, which was maintained until the third week in September, when a sudden decrease occurred. Thereafter, patients were seen sporadically until the third week in



Seasonal distribution of patients with epidemic pleurodynia admitted to the Boston City Hospital.

November, when the last patient was admitted. The monthly incidence of the disease at the Boston City Hospital during 1947 and a twelve year period from 1932 to 1943 inclusive is shown in the accompanying figure. Sylvest[3] and others have reported a similar seasonal incidence. The number of patients with the disease at the Boston City Hospital during the outbreak reported here must have far exceeded the number of patients in this series since it does not include many seen in the outpatient department.

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13. Finn, J. J.: Pleurodynia: Preliminary Note on an Epidemic in Boston, New England J. Med. **237**:621-623, 1947

Although the patients came from all sections of the city of Boston, the largest number were from the Roxbury area (33 per cent). Three patients were first taken ill outside of Boston (Lynn, Mass.; Randolph, Mass., and Bangor, Maine). At about this time there were reports of cases of a similar ailment from other parts of New England.

Table 1 shows the cases classified according to age and sex. The patients ranged in age from 3 to 69 years, but 80 per cent were less than 30 years old. Two patients gave histories of a similar ailment three years previously. Thirty-five per cent of the patients stated that one or more members of their family were suffering from an identical illness. In one instance 8 members of the same household were stricken within a period of one week.

CLINICAL FEATURES

Onset.—In over three fourths of the patients (76.2 per cent) the onset was sudden, with pain as the first symptom. Several of them

TABLE 1.—*Age and Sex Incidence in 114 Cases of Epidemic Pleurodynia*

Age	0-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	Total
Males	4	18	16	9	12	7	4	2	2	1	1	1	0	77
Females	0	8	11	5	5	4	2	0	0	1	0	0	1	37
Total	4	26	27	14	17	11	6	2	2	2	1	1	1	114

were stricken while at work. Not infrequently, the patient gave a history of having gone to bed feeling perfectly well, only to be awakened from sleep because of pain. Approximately one fourth (23.8 per cent) had prodromal symptoms which began one to ten days prior to the onset of pain; those of "head cold," headache, anorexia and myalgia were most frequently mentioned.

Symptoms.—In general, the onset of pain was accompanied with the other symptoms that were experienced or followed shortly by them, and prodromata, when present, became exaggerated. Table 2 summarizes the symptoms which were more commonly encountered.

Pain: All patients had pain which was typically sudden in onset. Rarely, a dull aching sensation was felt initially in the upper portion of the abdomen or at the costal margin, this being followed rapidly by the typical severe pleuritic type of pain which was described variously as "smothering," "stabbing," "knifelike," "catching" and "like a vise around the lower ribs." The pain was paroxysmal in type; complete freedom from pain between attacks occurred in the majority of cases. It was aggravated by deep breathing and in some patients by yawning, coughing, turning over in bed or walking. A few persons, particularly those with substernal pain, were unable to lie supine. The location of

the pain in 114 cases was as follows: chest only, 55; chest and abdomen, 42; abdomen only, 16, and lumbosacral region only, 1. The site of the thoracic pain in 97 persons is indicated in table 3. Except when limited to the substernal region, it was always felt over the lower ribs and for varying distances up the chest, usually on the lateral aspect but not infrequently over the front and back. Pain in the chest was referred in approximately one third of the cases (table 3). Of interest was the finding in 2 patients that substernal pain could be elicited when the examiner applied upward traction on the trachea. In 83 per cent of

TABLE 2.—*Symptoms Most Frequently Encountered in 114 Persons with Epidemic Pleurodynia*

Symptom	Number of Cases	Percentage Showing Symptom
Pain	114	100.0
Headache	50	43.8
Moderately severe	35	30.7
Very severe	15	13.1
Cough	38	33.2
"Dry"	24	21.0
Slightly productive	14	12.2
Anorexia	30	26.3
Nausea	27	23.6
Chilly sensations	24	21.0
Chills	21	18.4
"Head cold"	18	15.7
Vomiting	18	15.7
Sore throat	14	12.2
Diarrhea	8	7.0

TABLE 3.—*Location of Thoracic Pain and Site of Referral in 97 Cases**

Location of Thoracic Pain	No. of Cases	Referral of Thoracic Pain	No. of Cases
Right side only	23	Both shoulders	9
Left side only	19	Right shoulder	9
Substernal region only	6	Left shoulder	3
Substernal region and left side	1	Both scapulas	1
Substernal region and right side	3	Right scapula	1
Substernal region and both sides	10	Left scapula	2
Costal margins only	10	Interscapular region	5
Various combinations of areas	25	Neck	7
Total	97	Total	29

*It should be noted that 42 of the patients also had abdominal pain.

those with pain in the chest the symptom disappeared completely in less than eight days (table 4). Five patients suffered occasional recurrences of pain over varying periods up to five weeks after the onset.

Over half of the patients had abdominal pain which, like the thoracic pain, was typically sudden in onset and paroxysmal in character. However, in general, the abdominal pain was of shorter duration. The distribution of the pain in these cases is summarized in table 5.

Headache: Headache, when present, was usually of moderate severity and frontal in location. However, because of its severity during the prodromal stage of the illness in a number of cases an initial diagnosis of meningitis or encephalitis was considered.

Respiratory Symptoms: The cough, "dry" in character or productive of a small amount of whitish or yellowish sputum, was usually of short duration and troublesome chiefly because of the aggravation of the pain. Blood-streaked sputum was not observed.

Gastrointestinal Symptoms: Anorexia, when present, was of short duration in most instances and became manifest during the first day or two of the acute illness. However, several patients had anorexia, nausea and vomiting for one to three days prior to the onset of pain, and profound anorexia developed in 1 patient which lasted for one week after she had become afebrile. Nausea, vomiting, abdominal cramps and

TABLE 4.—*Time Interval Between Onset and Final Disappearance of Thoracic Pain*

Time in days	1	2	3	4	5	6	7	8	9	10	11	12	Over 12
No. of cases	11	11	12	14	14	6	11	3	4	3	1	3	4

TABLE 5.—*Location of Abdominal Pain in 58 Cases*

Site of Pain	No. of Cases
Epigastrium	19
Across upper part of abdomen	15
Right upper quadrant	8
Periumbilical region	5
Right lower quadrant	2
Across lower part of abdomen	2
Left upper quadrant	1
Right costovertebral region	1
Left costovertebral region	1
Various combinations of areas	4
Total	58

diarrhea developed in 1 patient twenty-four hours before the onset of thoracic pain, and the diarrhea continued for five days. In the other 7 patients with this symptom the diarrhea was mild and of twenty-four to forty-eight hours' duration.

Chills: Frank rigor or chilly sensations, when present, usually occurred during the first day of the illness. In several cases the second or third recrudescence of fever was immediately preceded by a shaking chill.

Miscellaneous Symptoms: Soreness or frank pain in the extremities, especially the legs, occurred in 11 cases, while "numbness" of the hands and feet occurred in 2. Prior to their admission to the hospital, 2 patients, 1 of whom was known to have epilepsy, had convulsions. Other

symptoms included retro-orbital pain (3 cases), vertigo (6 cases) and photophobia (1 case).

Physical Examination.—Pyrexia: One hundred and nine of the 114 patients were febrile during the period of observation, the maximum temperature ranging from 99 to 104 F., with a mean of 101 F. The total period of febrile manifestations varied from one to fourteen days, with a mean of three and a half days. Recrudescence of fever after return of the temperature to normal or near normal levels occurred one or more times in 63 cases. Such recrudescenses lasted about twenty-four hours and most often occurred from twenty-four to forty-eight hours after the preceding elevation of temperature. The pulse rate was proportional to the temperature.

Findings in the Chest: Visible splinting of the chest was a common finding, especially during the paroxysms of pain. A pleural friction rub was present in 28 cases (24.5 per cent). Friction rubs were first noted from the first to the twelfth day after onset of illness. They were heard on the right side in 14 cases, on the left in 11 and on both sides in 3. The rub in all instances was confined to the lower half of the chest and was almost invariably heard on either the lateral or the posterior aspect. Several of the patients were themselves aware of the rub, and occasionally it could be felt by the examiner. In some cases the rub was transient, lasting a few hours, whereas in others it persisted for as long as two weeks. Characteristically, patients with a rub complained at some time of pain in the chest. Localized tenderness to pressure was present in 28 cases, usually confined to the area of the chest where the pain was felt.

Abdominal Findings: While tenderness, confined to the abdomen (33 cases) or also in the chest (10 cases), was the most common finding, splinting and rigidity of the upper abdominal area were not infrequently present, especially when the pain was severe. In the 33 cases in which tenderness was confined to the abdomen, the actual site was the epigastrium (4), the periumbilical region (4), the right upper quadrant (14), both upper quadrants (6), the entire abdomen (1) or various locations (3). Transient splenomegaly was noted in 2 cases.

Lymphadenopathy: In 45 cases slight to moderate enlargement of one or more groups of lymph nodes was observed. This was confined to the cervical chains in 17 cases. The adenopathy was transient, and in only 4 cases was there slight tenderness of one or more nodes.

Other Findings: Slight to moderate pharyngitis occurred in 31 cases, while mild tonsillitis was observed in 14. Tenderness of one or both deltoid muscles was present in 4 patients, and tenderness of the calves was noted in 1. Slight conjunctivitis was noted in 10 cases, acute

delirium in 1, extreme drowsiness in 1 and slight nuchal rigidity in 3. Routine testing for cutaneous hyperesthesia was not done, but in 6 patients who were tested extreme hyperesthesia to pinprick over the lower costal and subcostal regions was experienced. One patient who felt a stinging sensation wherever the bedclothes touched her skin was found to have hyperesthesia over virtually the entire trunk and the extremities.

Roentgenographic examinations of the chest, done on 98 patients at various times after the onset of illness, revealed no abnormalities. Electrocardiographic tracings were taken on 51 patients at various times from two to fourteen days after the onset of illness. In 1 patient there were changes consistent with pericarditis and in 3 minor changes in the T waves and the S-T segments; the remainder of the tracings were normal.

Laboratory Findings.—One or more white blood cell counts were done for the majority of the patients; these are summarized in table 6. If 5,000 to 10,000 per cubic millimeter is taken as the normal range, approximately three fourths (76.7 per cent) of the patients had normal counts on the first day of the illness. Thereafter there was a tendency toward a progressive fall, most marked on the third and fourth day of the illness, when 25 and 21.4 per cent respectively of the patients examined showed definite leukopenia, with a white blood cell count below 5,000 per cubic millimeter. Forty-three of the 105 patients for whom differential counts were made had more than 3 per cent eosinophils at some stage of the illness, with 4 having 10 per cent or more. This tendency toward an elevated eosinophil count appeared about the fourth day of illness and continued well into the third week of convalescence. As many as 11 per cent atypical lymphocytes with vacuolated cytoplasm were noted in certain cases. No red cell inclusion bodies were observed.

One or more determinations of the erythrocyte sedimentation rate (Westergren method) were done for 72 patients; the results are summarized in table 7. Determinations of urinary diastase for 7 patients with epigastric pain showed normal levels.

Examinations of spinal fluid were done in 18 cases, in 4 of which there were abnormal findings, discussed later.

Complications.—Pericarditis: One patient had a typical pericardial friction rub when admitted on the seventh day of illness. The rub persisted during the following six days. Serial electrocardiograms gave a pattern consistent with the diagnosis of pericarditis.

Orchitis: Orchitis complicated the disease in 2 patients. One of these, aged 25, had an acute illness lasting six days, manifested by fever, pains in both legs, severe headache, paroxysmal pleuritic pain in the

TABLE 6.—*Summary of Hematologic Findings*

Day of Illness	1	2	3	4	5	6	7	8	9	10
Total leukocyte count										
Number of patients studied	43	17	20	28	17	16	17	9	6	4
Average count	8,672	7,470	6,325	6,848	7,223	7,789	7,041	7,399	7,400	7,788
Range	3,800 to 17,600	3,200 to 16,500	3,300 to 13,950	4,100 to 13,400	4,950 to 15,000	4,500 to 14,000	3,000 to 10,200	5,600 to 10,500	5,300 to 12,700	6,600 to 12,000
Percentage of patients with counts below 5,000/c. mm.	4.6	5.8	25.0	21.4	5.8	6.2	5.8	11.1	0	0
Differential leukocyte count										
Number of patients studied	41	15	21	24	15	14	12	6	9	4
Average percentage of neutrophils	73.5	69.2	67.1	66.3	61.4	62.2	61.0	57.5	59.6	56.7
Average percentage of lymphocytes	22.7	27.0	28.4	26.8	33.0	32.2	33.4	33.3	34.5	38.2

chest, vomiting and diarrhea. He was then asymptomatic for eight days. On the fourteenth day the right testicle became painful and swollen and the temperature rose to 100 F. These symptoms lasted three days. The second patient, [14] aged 25, first noticed painful swelling of the right testicle seven days after the onset of malaise, fever, headache, vertigo and paroxysmal epigastric pain markedly aggravated by breathing. A mild febrile reaction accompanied the onset of the orchitis, which subsided after five days. Two days later there developed pain and swelling of the left testicle, generalized myalgia, fever and arthralgia involving the spine, ankles, knees, wrists and the proximal interphalangeal articulations of the third and fourth fingers of the right hand. He was given sulfadiazine and was asymptomatic after five days. Both of the patients in whom orchitis developed gave histories of having had mumps during childhood, and there was no evidence to indicate that either patient had a venereal disease.

TABLE 7.—*Summary of Results of Determinations of Erythrocyte Sedimentation Rate (Westergren Method)*

	Day of Illness	No. of Determinations	Range	Average
Females (27 cases)	1 to 5	18	0 to 29 mm./hr.	16.5 mm./hr.
	6 to 10	12	4 to 70	24.1
	11 to 15	6	6 to 30	16.8
	16 to 20	7	5 to 28	17.5
Males (45 cases)	1 to 5	28	3 to 50	18.7
	6 to 10	14	3 to 40	19.6
	11 to 15	7	4 to 32	14.4
	16 to 20	16	0 to 25	9.0

Although the headache and other symptoms such as vertigo, photophobia, convulsions, delirium and nuchal rigidity suggested involvement of the central nervous system in a number of patients, only 4 of 18 persons on whom lumbar punctures were done had abnormal cerebrospinal fluid. In 1 case in which there were severe throbbing headache, pain in the legs and slight nuchal rigidity in addition to fever and pain in the chest, 140 cells per cubic millimeter (138 lymphocytes and 2 neutrophils) were present in the spinal fluid on the fifth day of illness. The sugar and protein levels of the fluid were normal, and cultural studies revealed no pathogens. By the eighteenth day of illness, the cells had decreased to 19 per cubic millimeter, all of which were lymphocytes. In a second case, with similar symptoms, there were 22 cells (18 lymphocytes, 2 monocytes and 2 neutrophils) in the spinal fluid and the sugar, protein and chloride levels were normal. The spinal fluid in 2 other cases was abnormal only in respect to the globulin content (68 and 48 mg. per hundred cubic centimeters).

Differential Diagnosis.—It was sometimes difficult to differentiate this malady from certain conditions requiring surgical treatment, espe-

14. This patient was seen through the courtesy of Dr. Leon Ryack.

cially in cases in which the pain was confined to the abdomen. Nine patients were admitted to the surgical wards, but only 1 was operated on; no abdominal abnormality was found. As the epidemic progressed, typical cases presented no difficulty in diagnosis. However, there was a small group, not included in the present series, in which symptoms of involvement of the central nervous system predominated and pleuritic pain was minimal or absent. In them, differentiation from the nonparalytic form of anterior poliomyelitis was impossible and various encephalitides of virus origin could not be eliminated. During the outbreak of pleurodynia, 7 patients with headache, fever, nuchal rigidity and no pain in the chest were observed. The cerebrospinal fluid was examined in 5 cases, and in 3 of these there was pleocytosis. None of these patients experienced motor weakness. It may be significant that 1 of them was the mother of a patient sick at the same time with typical pleurodynia.

Treatment.—The treatment was symptomatic in the great majority of cases. Penicillin was given to 15 patients and streptomycin to 1, with no alteration in the course of the disease.

Etiologic Studies.—Cultural and Serologic Tests: Blood cultures from 65 patients taken at various times during the first ten days of the illness contained no pathogens. Cultures from the throats of 38 patients revealed no predominant organism. In guinea pigs inoculated with gastric aspirations from 6 patients no evidence of tuberculosis was found.

Determinations of heterophile antibodies were carried out on paired serums from 57 patients, collected in the acute and convalescent phases of the disease, while tests for cold autohemagglutinins and influenza A and B antibodies (hemagglutinin-inhibition test) were done on similar pair of serums from 39 patients; no significant changes in titer were observed. Serums from a smaller number of patients did not contain significant concentrations of agglutinins for Salmonella typhosa, Salmonella schottmülleri, Brucella aborus, Pasteurella tularensis or Proteus OX 19.

Complement fixation tests for mumps and neutralization tests for lymphocytic choriomeningitis were done on the serums of 2 patients with severe headache, pleural pain and nuchal rigidity, 1 of whom had pleocytosis; the results were negative. The reaction to the complement fixation test for mumps was also negative, when it was performed on serums in the acute and convalescent phases of the disease, in 2 patients in whom orchitis developed and in 8 additional patients with uncomplicated pleurodynia.

TABLE 8.—*Procedures Employed in Attempts to Isolate the Agent of Epidemic Pleurodynia in Chick Embryos*

Patient	Material	Interval Between Onset of Illness and Collection of Specimen, Days	Storage of Material	Age Eggs Used, Days	Route of Inoculation	Passages	Passage Interval, Days	Tests for Presence of Virus
Kl.	Throat Washing	2	Fresh	6 to 7	Amniotic	4	7	Complement fixation: 1st, 3rd, 4th passages, amniotic fluid and embryo. Hemagglutination: 1st, 2nd, 3rd, 4th passage amniotic fluid
Dm.	Throat Washing	2	Stored in carbon dioxide 12 days	5 to 7	Amniotic	4	7	Complement fixation: 4th passage, amniotic fluid and embryo. Mice: 4th passage, embryo intracerebrally to 5 mice
De.	Throat Washing	2	Fresh	5	Amniotic	7	7	Complement fixation: 6th passage, amniotic fluid and embryo. Hemagglutination: 6th passage, amniotic fluid. Mice: 6th passage, embryo intracerebrally to 5 mice. Skin test: 5th passage, amniotic fluid
Mc.	Throat Washing	2	Stored in carbon dioxide 28 days	5	Amniotic	7	7	Complement fixation: 7th passage, amniotic fluid and embryo. Hemagglutination: 6th passage, amniotic fluid. Mice: 7th passage, embryo intracerebrally to 5 mice
Ko.	Throat Washing	3	Stored in carbon dioxide 27 days	6	Amniotic	5	7	Complement fixation: 5th passage, amniotic fluid and embryo. Hemagglutination: 5th passage, amniotic fluid. Mice: 5th passage, embryo intracerebrally to 5 mice. Skin test: 3rd and 4th passage, amniotic fluid
Bl.	Throat Washing	1	Stored in carbon dioxide 24 days	4 to 5	Amniotic	7	7	Complement fixation: 7th passage, amniotic fluid and embryo. Hemagglutination: 7th passage, amniotic fluid. Mice: 7th passage, embryo intracerebrally to 5 mice. Skin test: 4th passage, amniotic fluid
Mc.	Cerebrospinal Fluid	2	Fresh	5	Yolk sac, then amniotic	4	5-7	Complement fixation: 4th passage, embryo. Hemagglutination: 1st passage, amniotic fluid

Kl.	Defibrinated blood	2	Fresh	6 to 7	Yolk sac	4	7	Complement fixation: 4th passage, yolk sac. Hemagglutination: 4th passage, yolk sac
Bl.	Defibrinated blood	1	Fresh	6	Amniotic	4	7	Complement fixation: 4th passage, embryo
Dm.	Defibrinated blood	2	Stored in carbon dioxide 12 days	5 to 7	Yolk sac	4	7	Complement fixation: 4th passage, yolk sac
Ko.	Defibrinated blood	3	Stored in carbon dioxide 27 days	6	Yolk sac	4	7	Complement fixation: 4th passage, yolk sac. Hemagglutination: 3rd passage, amniotic fluid
De.	Stool	2	Fresh	5	Amniotic	7	7	Complement fixation: 6th passage, embryo and amniotic fluid. Hemagglutination: 6th passage, amniotic fluid. Mice: 6th passage, embryo intracerebrally to 5 mice

ATTEMPTS TO ISOLATE THE ETIOLOGIC AGENT

I. Specimens Employed.—Throat washings in 10 per cent horse serum broth, clotted and defibrinated blood, cerebrospinal fluid and rectal swabs were collected from typical patients during the acute phase of the illness. These materials were used within a few hours or were sealed in glass tubes and stored in the carbon dioxide ice box. In all, throat washings from 6 patients, blood specimens from 4 patients and one specimen of cerebrospinal fluid and one of stool were utilized. The data concerning the collection and storage of these materials are summarized in table 8.

II. Experiments Utilizing Embryonated Hen's Eggs.—(1) Technic of Inoculation and Passage: Throat washings were mixed in 0.8 cc. amounts with 1 cc. of penicillin solution and 0.2 cc. of streptomycin solution, so that each 0.1 cc. of the resulting mixture contained 500 units of penicillin G and 0.5 mg. of streptomycin base. In early experiments this mixture was centrifuged at 1,000 revolutions per minute for two minutes and the supernatant fluid then inoculated in 0.1 cc. amounts intra-amniotically. Bacteria were usually adequately controlled by this procedure, but unidentified species of Candida occasionally grew in the eggs as a troublesome contaminant. Accordingly, in subsequent experiments centrifugation at 2,860 revolutions per minute for thirty minutes in a Sorvall angle centrifuge was employed; thereafter no difficulty with yeasts was encountered. In the experiments listed in table 8 no contamination with bacteria or yeasts occurred. The intra-amniotic inoculations were carried out on eggs incubated four to seven days at 38 C. Passages were carried out at seven day intervals by pooling the individual embryos and the amniotic fluid from each egg with sufficient isotonic sodium chloride solution to make a 20 per cent suspension by weight. This was ground with alundum and centrifuged for three minutes at 1,000 revolutions per minute, and 0.1 cc. of the supernatant fluid was passed intra-amniotically to each egg; in the majority of passages, antibiotics were also inoculated into the yolk sac in concentrations similar to those used originally. In most instances from ten to fourteen eggs were employed in each passage. All inoculated eggs were incubated at 35 C.

Defibrinated blood was inoculated intra-amniotically in 0.05 cc. amounts in one experiment and passed as described; in three experiments 0.25 cc. was inoculated into the yolk sac and passages were made by the same route, 0.4 to 0.75 cc. amounts of a 20 per cent yolk sac suspension in isotonic sodium chloride solution being used. With a single exception, antibiotics were not employed in these experiments. Cerebrospinal fluid from 1 patient was inoculated in 0.5 cc. amounts into the yolk sac and subsequently passed via the amniotic route, a

20 per cent suspension of embryo and amniotic membrane being utilized. The single specimen of stool studied was collected by means of a rectal swab and the material emulsified in a 50 per cent broth—isotonic sodium chloride solution containing antibiotics in the same concentration as was used in the studies of throat washings; the suspension was centrifuged for thirty minutes at 2,860 revolutions per minute in the Sorvall angle centrifuge and 0.1 cc. inoculated intra-amniotically. Antibiotics were employed throughout the subsequent passages, in part via the yolk sac and in part via the intra-amniotic route.

(2) Tests Used in Attempting to Detect the Presence of Virus in the Egg Passage Material: Daily mortality records were kept, and the embryos and membranes were examined for gross lesions at each passage. Other examinations for the presence of an etiologic agent were carried out as indicated in table 8. Complement fixation tests were performed as previously described.[15] In each test the pooled amniotic fluids and the pooled embryos from one passage were used separately in a 20 per cent suspension in isotonic sodium chloride solution as antigens and were set up with four pairs of serums collected from patients in the acute and convalescent stages of the illness. The serums had been collected at intervals of two to four weeks, and each was used in dilutions of 1:2 and 1:8. As an additional control, a parallel system, employing mumps antigen and homologous antiserums, was set up at the time each test was carried out.

The amniotic fluids were examined for the presence of hemagglutinins, with the use of both hen and human type "O" cells. Subinoculations of the egg passage material, which had been stored in sealed glass tubes in solid carbon dioxide for seven to forty-one days, in newly weaned mice in doses of 0.03 cc. intracerebrally were carried out as indicated in table 8; the mice were observed over a thirty day period. Further passages were not made.

The possibility that infection in the egg might be detected by employing the egg fluid as a skin-testing antigen was investigated. Three pools of amniotic fluids from throat-washing experiments (see table 8) and a pool of normal amniotic fluid were sealed in glass ampules, heated at 60 C. for thirty minutes and then diluted 1:5 in isotonic sodium chloride solution. After sterility tests, each lot was given intradermally in 0.1 cc amounts to each of four persons who had been sick from five to eight weeks earlier with epidemic pleurodynia and to 2 control patients. Readings of the intradermal reactions were made at thirty

15. Enders, J. F., and Levens, J. H.: Mumps, in Diagnostic Procedures for Virus and Rickettsial Diseases, New York, American Public Health Association, 1948, pp. 139-164.

minutes, at twenty-four, forty-eight, seventy-two and ninety-six hours, and at one week. No significant cutaneous response was observed.

(3) Results of Experiments Employing Fertile Eggs: The studies outlined here gave uniformly negative results. No evidence was obtained that the etiologic agent had been isolated in embryonated eggs.

III. Experiments Utilizing Mice.—Methods and Results: Fresh throat washings from 1 patient were mixed with antibiotics as in the egg experiments and given intranasally in 0.05 cc. amounts to young mice (3 to 4 weeks old). In two experiments fresh defibrinated blood was given intracerebrally in 0.03 cc. amounts to young mice. No symptoms appeared over the course of a month, and no passages were made.

Throat washings from 4 different patients which had been stored for approximately three months were each given intracerebrally to one litter of 10 day old suckling mice; prior to use, antibiotics were added to each specimen and the material was centrifuged in the Sorvall centrifuge. Three of the litters showed no symptoms, but in the litter inoculated with specimen "Mc" 4 of 8 mice died between the seventh and the thirteenth day, and on removal the brains were bacteriologically sterile. These were passed from two to six times in suckling mice, with no similar mortality in the subsequent passages. The mortality with specimen "Mc" could not be explained; it was again inoculated into a litter of suckling mice and was carried three passages at thirteen day intervals, with negative results.

COMMENT

This study of 114 cases of epidemic pleurodynia emphasizes the diverse manifestations of the disease. During the outbreak, many of the less common manifestations and several of the complications mentioned by previous observers were seen.

Whereas approximately one fourth of the patients in the present series had prodromal symptoms, the majority of the previous observers have commented on the lack of prodromes or have failed to mention them. Likewise, signs of involvement of the respiratory tract, noted in a significant percentage of cases, were not found by most earlier observers, although evidence of mild pharyngitis was found in over three fourths of the cases observed by Howard and others[12] and in virtually all the cases observed by Fulghum.[16] Lymphadenopathy, seen in this series, as far as is known has not been previously described.

The tendency toward leukopenia, which was most marked on the third to the fourth day of the illness, is comparable to that observed

16. Fulghum, C. B.: Epidemic Pleurodynia, J. M. A. Georgia **31**:63-65, 1942.

by MacDonald and others[9] and McConnell.[10] Eosinophilia has not been stressed in reports of outbreaks of pleurodynia in the United States, although most medical textbooks mention it as a frequent phenomenon, especially during convalescence. Perhaps the number of cases with eosinophilia would have been greater in the present series had more patients been tested during convalescence. No correlation could be established between eosinophilia and the presence or absence of a plural friction rub.

The number of cases in which a pleural friction rub developed was relatively high but not exceptional. Although orchitis complicating the disease has been mentioned in a few epidemics,[17] the 2 cases in this series are the first reported from the United States. Pericarditis as a complication of pleurodynia has been observed only once previously in the United States[18] and only infrequently elsewhere. Manifestations in the central nervous system were mentioned only casually in earlier reports, but observations by Howard and others[12] and McConnell[10] together with those of the present study suggest that involvement of the nervous system is not uncommon.

Efforts to isolate a virus from certain of the cases described in the present outbreak were unsuccessful. Negative results were also obtained at the National Institute of Health when materials obtained from the present outbreak were employed.[11] The various bacteriologic and serologic studies that were done added no information regarding the etiology of epidemic pleurodynia.

SUMMARY

1. The clinical features of 114 cases of epidemic pleurodynia observed at the Boston City Hospital during the summer of 1947 are presented.

2. Complications of the disease encountered included involvement of the central nervous system, orchitis and pericarditis.

3. The laboratory investigations which were carried out in an effort to isolate an etiologic agent are summarized.

Miss Alice H. Northrop, Miss Mona Katz and Mrs. Mildred Barnes rendered technical assistance.

17. Jamieson, W. M., and Prinsley, D. M.: Bornholm Disease in the Tropics, Brit. M. J. **2**:47-50, 1947.

18. Locke, E. A., and Farnsworth, D. L.: The Clinical Characteristics of Epidemic Pleurodynia, Tr. A. Am. Physicians **51**:399-406, 1936.

PURPURA HEMORRHAGICA ASSOCIATED WITH SARCOIDOSIS

CHARLES A. RIBAUDO, M.D.
THOMAS J. GILLIGAN, M.D.
AND
ANTONIO ROTTINO, M.D.
NEW YORK

IN THE extensive review articles[1] concerning sarcoidosis which have appeared during the last twelve years no mention is made of purpura as an important finding. In his discussion of purpura, Wintrobe[2] did not list sarcoid disease as a recognized cause. Dameshek,[3] in his writings, mentioned the two diseases in association with one another. There have been a few cases reported in which both diseases were found. Enzer,[4] for instance, described a case of Boeck's sarcoid and purpura in which the diagnosis was later confirmed by autopsy. Rubin and Pinner[5] reviewed cases of sarcoidosis in which autopsy had been performed and found 1 case in which thrombocytopenic purpura was responsible for death.

From St. Vincent's Hospital.

1. (*a*) Longcope, W. T.: Sarcoidosis, or Besnier-Boeck-Schaumann Disease: Frank Billings Lecture, J. A. M. A. **117**:1321 (Oct. 18) 1941. (*b*) Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**:223, 1937. (*c*) Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis, Am. Rev. Tuberc. **49**:289, 1944. (*d*) Hunter, F. T.: Hutchinson-Boeck's Disease (Generalized Sarcoidosis), New England J. Med. **214**:346, 1936. (*e*) Harrell, G. T.: Generalized Sarcoidosis of Boeck: Clinical Review of Eleven Cases, with Studies of Blood and Etiologic Factors, Arch. Int. Med. **65**:1003 (May) 1940. (*f*) McCort, J. J.; Wood, R. H.; Hamilton, J. B., and Ehrlich, D. E.: Sarcoidosis: A Clinical and Roentgenologic Study of Twenty-Eight Proved Cases, ibid. **80**:293 (Sept.) 1947.

2. Wintrobe, M. M.: Clinical Hematology, ed. 2, Philadelphia, Lea & Febiger, p. 611.

3. Dameshek, W., and Miller, E. B.: The Megakaryocytes in Idiopathic Thrombocytopenic Purpura: Form of Hypersplenism, Blood **1**:27, 1946. Dameshek, W., and Estren, S.: The Spleen and Hypersplenism, New York, Grune & Stratton, Inc., 1947.

4. Enzer, M.: Case Report of Boeck's Sarcoid and Purpura, Am. J. Path. **22**:663, 1946.

5. Rubin, E. H., and Pinner, M.: Sarcoidosis, Am. Rev. Tuberc. **49**:146, 1944.

In a group of 30 cases in which splenectomy was performed for thrombocytopenia Schwartz[6] found one instance of sarcoid spleen. Nordland and his associates[7] cited an example of a pregnant woman relieved of purpura hemorrhagica after the removal of a sarcoid spleen.

Because of the apparent rarity of the association of these two diseases, we feel it to be of interest to report 2 cases which came to our attention within the relatively short period of seven months in one hospital.

CASE 1.—An 18 year old Negro woman was admitted to St. Vincent's Hospital, New York, on July 22, 1947, complaining of nosebleeds and of purplish swelling on the left side of the lower lip of two days' duration. The patient's illness had begun eleven weeks before her admission with bilateral, nontender periauricular swelling. On the same day she had also noted the appearance of brownish raised areas about the ankles. During the next three weeks she was febrile, her temperature rising each night to 100.6 F. Thereafter the swelling and the temperature gradually subsided, but the rash became more widespread and, one week before admission, turned purple. Two days before her admission the first bleeding from the nose and mouth occurred, and ecchymosis appeared on the left side of the lower lip. Her urine was red on the day she was admitted. The last menstrual period had occurred twelve days before, lasted the usual four days and was scant in amount.

There was nothing noteworthy in her own history or in the family history. She had had mumps at the age of 4, had undergone uneventful tonsillectomy in 1944 and had had incomplete abortion in 1947, which was completed at St. Vincent's Hospital on March 22, 1947, by dilation and curettage, accompanied with no unusual bleeding. Drugs ingested during the past year had included feosol[R] (exsiccated ferrous sulfate in an inert vehicle) tablets, one ampule of alphahypophamine (pitocin[R]) and one of ergonovine maleate (ergotrate[R]) during her stay in the hospital in March and penicillin orally for three days and sodium bicarbonate for eleven days, both during early May.

Physical examination showed her to be well developed, well nourished and without apparent illness. Her temperature was 100.6 F., the pulse rate 76, the respiratory rate 20 and the blood pressure 120 systolic and 80 diastolic. The skin of her legs and thighs was covered with a diffuse, multiform, slightly raised purple eruption, with rectangular individual lesions of about 1 by 0.5 cm. They did not blanch on pressure. There were roughly oval areas 0.5 cm. in diameter on the dorsum of the forearms and occasional pinpoint purple spots in the same area. The buttocks had numerous purple-black areas the size of a pinhead. There were two hemorrhages occupying about one half of the lower portion of the right bulbar conjunctiva. The fundi were normal. There was an ecchymotic area about 2 cm. in diameter on the left side of the lower lip.

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6. Schwartz, S. O.: The Prognostic Value of Marrow Eosinophils in Thrombocytopenic Purpura, Am. J. M. Sc. **209**:579, 1945.

7. Nordland, M.; Ylvisaker, R. S.; Larson, P., and Reiff, R.: Pregnancy Complicated by Idiopathic Thrompocytopenic Purpura and Sarcoid Disease of the Spleen: Splenectomy and Subsequent Normal Delivery, Minnesota Med. **29**:166, 1946.

There were numerous pinpoint petechial hemorrhages on the tongue, and small fresh bleeding points were noted on the gums and the posterior pharyngeal wall. There was no lymphadenopathy of note, and the spleen was not palpable.

Laboratory examinations showed the urine to contain numerous red blood cells and albumin (2 plus). On July 22 the hemoglobin content was 11.6 Gm. per hundred cubic centimeters, the red blood cell count 3,710,000 per cubic millimeter and the white blood cell count 8,400, of which 64 per cent were polymorphonuclear leukocytes, 3 per cent metamyelocytes, 30 per cent lymphocytes and 3 per cent monocytes. The platelet count was 570,000. The red cells showed moderate achromia and anisocytosis. The prothrombin time according to the Shapiro method was seventeen seconds (undiluted) and forty seconds (diluted).

The blood serum bilirubin level was 1.4 mg., the serum albumin level 3.75 mg. and the serum globulin level 2.1 mg. per hundred cubic centimeters. The bleeding time was five minutes and the clotting time five and a half minutes.

On the patient's admission to the hospital, blood culture and a Kahn test of the blood revealed no organisms.

On July 25 the hematocrit value was 24 mm., the serum bilirubin content 1.1 mg. per hundred cubic centimeters and the blood urea nitrogen level 12 mg. The clot retraction in twenty-four hours was good, and a tourniquet test showed no petechiae. Reaction to a Mantoux test was negative in a 1 to 100,000 dilution.

On July 26 the bleeding time had risen to forty minutes and the clotting time was one and a half minutes. The tourniquet test still showed no petechiae. The red blood cell count was 3,200,000 per cubic millimeter, the hemoglobin content was 6 Gm. per hundred cubic centimeters and the white blood cell count was 12,000 per cubic millimeter.

On July 28 the serum bilirubin content was 0.9 mg. and a preparation examined at three, six, twenty-four and forty-eight hours revealed no trace of sickling. The following day the serum bilirubin content rose to 3.1 mg. The tourniquet test showed 10 petechiae in a 2 cm. field. The prothrombin time remained seventeen seconds (undiluted) and forty-one seconds (diluted).

A roentgenogram of the chest showed massive bilateral hilar adenopathy, with clear parenchyma and normal diaphragmatic contours.

Aspiration of sternal marrow showed the following count: polymorphonuclear leukocytes, 39 per cent; lymphocytes, 19 per cent; metamyelocytes II, 14 per cent; monocytes, 13 per cent; myelocytes, 14 per cent; reticulum cells, 1 per cent; megakaryoblasts, 3 per cent; megakaryoctes, 1 per cent; normoblasts, 13 per cent, and erythroblasts, 18 per cent. The monocytes were large and vacuolated and contained phagocytosed material.

When admitted, the patient, although oozing slight amounts of blood from nose and gums, did not appear seriously ill. However, the oozing continued, the urine became grossly bloody, her temperature fluctuated daily between 101 and 103 F. and she began to lose ground. Transfusions were given on the fifth and sixth days, but no improvement resulted. On the seventh day she appeared mentally confused and her skin showed widely scattered ecchymosis. On the eighth day incomplete hemiplegia affecting the left side developed, and she died in semicoma. A diagnostic lumbar puncture showed grossly bloody spinal fluid under 600 mm. of water pressure. The patient had

no bleeding into the points, and the stools were not tarry during her stay in the hospital.

Autopsy showed numerous ecchymoses up to 2 cm. in diameter in the skin

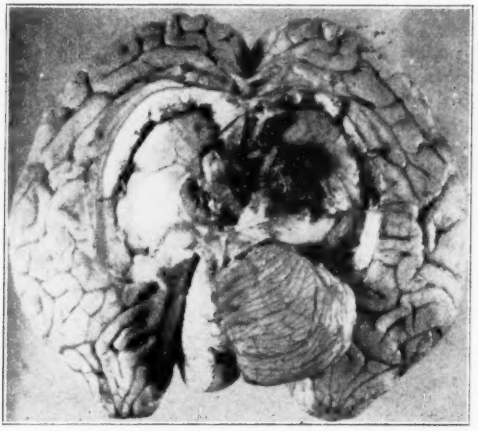

Fig. 1.—Brain, hemorrhage into the right corpora striatum.

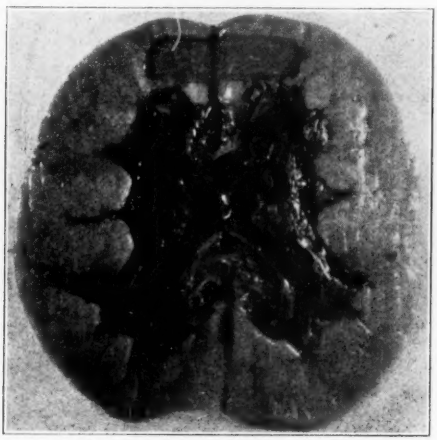

Fig. 2.—Extensive peripelvic hemorrhage of kidney.

over the entire body as well as in mucous membrane of the mouth. There was 200 cc. of fluid blood within the peritoneal cavity, and a large hematoma occupied the leaves of the mesentery of the small bowel and the retroperitoneum

of the right lateral gutter. Small hemorrhages were noted in the pericardium, epicardium and pleurae.

Examination of the brain revealed a hematoma 2.5 by 2 cm. (fig. 1). It occupied the right thalmus and extended down into the peduncle of the same side.

Fresh hemorrhage was evident in scattered lobules in both lungs.

Grossly the heart appeared normal except for epicardial and endocardial hemorrhages.

The spleen was not enlarged but appeared mushy, and it was deep red.

Fig. 3.—Heart-lung preparation. Note mass of large nodes beneath the tracheal bifurcation.

The kidneys were extremely pale. Diffuse and extensive hemorrhage was seen in the pelvis and in the peripelvic tissue (fig. 2).

Small submucosal hemorrhages were noted in the esophagus and the stomach. The same was true of the uterine mucosa. The gross appearance of the adrenals, pancreas, liver and gallbladder was normal.

About the trachea and the main bronchi was a large cluster of solid, gray, firm, nonfused lymph nodes measuring up to 3 cm. in diameter (fig 3).

The microscopic examination indicated that, in addition to the gross hemorrhages already described, the pathologic process responsible for the enlargement

of the lymph nodes was sarcoidosis. In the interstitium of the myocardium were numerous small granulomas composed of a loose fibrous stroma, lymphocytes, large mononuclear cells and occasional giant cells. The small granulomas were found scattered throughout the lung and spleen. Many small adenomas were seen in the adrenal gland, together with hypertrophy of the zona fasciculata. The bone marrow presented a hyperplastic appearance. Megacaryocytes were plentiful, and many appeared degenerated.

The anatomic diagnosis was sarcoidosis of the mediastinal lymph nodes, lungs, spleen and myocardium; hemorrhage into the right thalmus, the left putamen and both lateral ventricles; generalized purpura of the skin, and hemorrhage into the pericardium, epicardium, endocardium, pelvis of both kidneys, mucosa of the urinary bladder, stomach, small intestine and retroperitoneum.

Case 2.—Mrs. A. R., aged 23, was first seen on Dec. 17, 1947, for a routine check-up. She had no complaints. Her past history showed that menses had started at the age of 12, occurred every twenty-eight days and lasted three to five days. She had had menorrhagia of such severity that it necessitated hospitalization on four occasions since 1942. During the last hospitalization, in February 1947, dilation and curettage were done, but this did not contribute to the diagnosis. The menorrhagia ceased spontaneously on administration of blood transfusions. During one period between hospitalizations her physician gave her injections of male hormones in doses producing hypertrichosis; during another period he gave her estrogens. Neither of these forms of therapy had any apparent influence on her general condition. Since the age of 16 the patient had noticed recurrent, spontaneous ecchymosis, nontraumatic, on her thighs, legs, arms and hands. Inguinal herniorrphaphy was done on the right side at the age of 5. There was no history of allergy.

At the time of the physical check-up under discussion nothing abnormal was found. Laboratory examination of the blood showed the hemoglobin content to be 89 per cent, or 15.13 Gm. per hundred cubic centimeters. The red cells numbered 5,000,000, the color index was 0.89 and the white cells numbered 8,600, with a differential count of 59 per cent polymorphonuclear leukocytes, 1 per cent eosinophils, 2 per cent monocytes and 38 per cent lymphocytes. The platelet count was 100,000 per cubic millimeter, the clotting time three and a half minutes and the bleeding time two and a half minutes. The urine was normal.

During the month of January 1948, the patient noted numerous areas of ecchymosis on the right arm, left index finger and right middle and little fingers. At this time the laboratory examinations showed the prothrombin time to be fourteen seconds (undiluted). The hemoglobin content was 78 per cent, (13.26 Gm. per hundred cubic centimeters), the color index 0.89, the red blood cell count 4,400,000, with slight hypochromia and anisocytosis, and the white blood cell count 7,700, with a differential count of 67 per cent polymorphonuclear leukocytes, 1 per cent eosinophils, 6 per cent monocytes and 26 per cent lymphocytes. The platelet count was 110,000.

The patient was admitted on Feb. 4, 1948, to St. Vincent's Hospital. Physical examination showed moderate hypertrichosis of the face. The heart and lungs were normal, the spleen was just palpable below the left costal border and there were fading ecchymotic areas on the dorsum of both hands and the left elbow.

Laboratory examination of sternal marrow on February 4 showed hyperplasia of the megakaryocytes, with numerous young forms. Differential study of the bone marrow showed 48 per cent polymorphonuclear leukocytes, 5 per cent metamyelocytes II, 5 per cent megakaryoblasts, 14 per cent lymphocytes, 2 per cent normoblasts, 19 per cent myelocytes and 2 per cent lymphoblasts. Examination of blood showed the red cells to be 4,700,000, with a hemoglobin content of 96 per cent, and the white cells 8,050, with 50 per cent neutrophils, 8 per cent metamyelocytes II, 3 per cent eosinophils, 34 per cent lymphocytes and 5 per cent monocytes. The platelet count was 192,000.

On February 5 the bleeding time was seven and a half minutes and the prothrombin time eighteen seconds. The blood was Rh positive and of type O, the blood calcium content was 9.5 mg. and the phosphorus content 3.2 mg. per hundred cubic centimeters. Clot retraction was normal, and the capillary fragility test revealed nothing unusual. On February 9 the platelet count was 170,000. On February 10 splenectomy was done in the usual manner. The spleen was found to be slightly enlarged and adherent to the stomach and diaphragm.

Pathologic examination of the removed spleen revealed the presence of sarcoid disease. The postoperative convalescence was uneventful. Roentgenograms of the lungs and of the bones of the hands revealed no evidence of sarcoid disease, and no cutaneous lesions were observed at any time. No further purpura was noted.

On February 13, two days after the operation, laboratory examination showed the platelet count to be 260,000. On February 16, five days postoperatively, the platelet count was 329,000, the hemoglobin content 100 per cent, the red blood cell count 4,910,000 and the white blood cell count 18,750. The differential count showed 67 per cent polymorphonuclear leukocytes, 7 per cent metamyelocytes II, 1 per cent basophils, 2 per cent eosinophils, 11 per cent lymphocytes, and 12 per cent monocytes. Total serum protein amounted to 6.5 mg. per hundred cubic centimeters, with serum albumin 4 per cent and serum globulin 2.5 per cent. The reaction to the Mantoux test was negative in dilutions of 1:10,000 and 1:100.

The patient was discharged on the eleventh postoperative day in good condition. No further purpura was noted.

The first menstrual period after splenectomy occurred on Feb. 25, 1948, and ceased on March 2, 1948. Only two to three napkins daily were required, whereas formerly six to eight had been necessary.

On March 8, 1948, a roentgenogram of the chest was normal. On March 15 laboratory examination of the blood showed the hemoglobin content to be 75 per cent, the red blood cell count 4,500,000 and the color index 0.83. Moderate hypochromia and anisocytosis were present. The white cells numbered 11,200, with a differential count of 70 per cent polymorphonuclear leukocytes, 2 per cent metamyelocytes II, 3 per cent eosinophils, 5 per cent monocytes and 20 per cent lymphocytes. The platelet count was 140,000.

The patient had no more evidence of purpura, in spite of the recurrence of a low platelet count, and was asymptomatic.

COMMENT

The cases described in this paper are reported chiefly because of the rarity of the association of purpura hemorrhagica and sarcoidosis. Only 4 cases have been reported in the literature. In addition to these, Dameshek[8] mentioned 2 other cases in which sarcoid lesions were found in the spleen after extirpation for purpura hemorrhagica.

In our first case sarcoidosis suggested itself as a diagnosis because of the mediastinal shadow and the fact that in a patient who had had mumps at the age of 4 years parotitis was found to have occurred two months prior to the onset of her present illness. This case was atypical in that superficial adenopathy was absent. Several authors emphasize the fact that there is association of superficial adenopathy and enlargement of mediastinal lymph nodes in almost 100 per cent of cases.

The rapid decline in this patient's condition made it possible to do only a single Mantoux test in a dilution of 1:100,000, which gave a negative reaction. In the second case the Mantoux tests in dilutions of 1:10,000 and 1:100 gave negative reactions.

The other laboratory finding frequently reported in sarcoidosis is the elevation of the globulin fraction of the serum protein. In the cases presented the total protein and globulin fractions were normal and consequently not contributory to the clinical diagnosis.

The roentgenogram of the chest in case 1, showing bilaterally enlarged, discrete, lobulated hilar nodes, suggested both sarcoidosis and malignant lymphoma. Time did not permit repeated roentgenologic study of the chest. In the second case the roentgenogram of the chest was essentially normal. Cystic changes in small bones, reported in 25 per cent of cases of sarcoidosis, were not present in either of our cases.

Hematologic studies of cases of sarcoidosis have yielded various findings from normal red and white blood cell counts to leukopenia and eosinophilia. However, Dameshek[3] mentioned sarcoidosis as being associated with hypersplenism and thrombocytopenia. In case 1 the bleeding and coagulation times were at first normal, as were the prothrombin time and the clot reaction time. There was no sickling phenomenon, and the platelet count of the peripheral blood was 500,000. However, the bleeding time became prolonged and the reaction to the capillary fragility test positive, and these factors combined with the megakaryocytic hyperplasia of the bone marrow suggested an abnormality of the platelet mechanism allied to thrombocytopenia purpura. With the repeated low

8. Dameshek, W.: Personal communication to the authors.

platelet counts, the slightly increased bleeding time and the characteristic clinical findings, the second case was undoubtedly one of thrombocytopenic purpura and sarcoidosis.

SUMMARY

Two cases of hemorrhagic purpura are presented in both of which, as proved by autopsy and operation respectively, the condition was associated with sarcoidosis. In our opinion the connection between sarcoidosis and hematologic disorders deserves further investigation.

PATHOGENESIS OF CIRCULATORY FAILURE IN ROCKY MOUNTAIN SPOTTED FEVER

Alterations in the Blood Volume and the Thiocyanate Space at Various Stages of the Disease

GEORGE T. HARRELL, M.D.
AND
JERRY K. AIKAWA, M.D.
WINSTOM-SALEM, N. C.

PERIPHERAL circulatory failure is an important complication of Rocky Mountain spotted fever. Previous studies have shown that the collapse occurs usually in the second week of rash and that the disturbance can be alleviated by the administration of preformed protein.[1] The mechanism responsible for the circulatory changes is obscure, but the peripheral collapse is accompanied with a drop in serum proteins and with the development of visible generalized edema.[2] The resemblance of the clinical picture to "shock" suggests that a drop in the circulating blood volume occurs.

The present studies were undertaken to determine whether the blood volume is altered, to observe the time at which the changes develop and to correlate the magnitude of the alterations with the clinical picture and other pertinent laboratory data. Determinations of the plasma volume and the thiocyanate space were done serially in a group of patients with rickettsial spotted fever, and the effects of supportive and specific therapy on the altered distribution of the fluid were observed.

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From the Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital.

1. Harrell, G. T.; Wolff, W. A.; Venning, W. L., and Reinhart, J. B.: The Prevention and Control of Disturbances of Protein Metabolism in Rocky Mountain Spotted Fever, South. M. J. **39**:551-558 (July) 1946.

2. Harrell, G. T.; Venning, W. L., and Wolff, W. A.: The Treatment of Rocky Mountain Spotted Fever, with Particular Reference to Intravenous Fluids: A New Approach to Basic Supportive Therapy, J.A.M.A. **126**:929-934 (Dec. 9) 1944.

CLINICAL STUDY

Material.—The 13 cases presented were studied between June and October 1946. Seven of the patients were adults, and 6 were children; most of them were in the North Carolina Baptist Hospital, but several were in hospitals in nearby towns.[3] Additional patients have been similarly studied, but these 13 cases have been selected for presentation because each one illustrates some principle we wish to bring out.

The diagnosis of Rocky Mountain spotted fever was made on the basis of the history and the physical signs and was later confirmed by serologic tests. The cases are classified roughly according to the clinical severity of the disease and are further subdivided according to the type of treatment received. Seven patients received supportive therapy only, and 6 received, in addition, specific therapy. The distribution of cases according to clinical severity was approximately the same in the two groups.

CLASSIFICATION OF CASES

Therapy	Clinical Severity*				Total Cases
	Mild	Moderate	Severe	Fatal	
Supportive only*	2	4, 7	1, 8	3, 12	7
Specific and supportive*	5, 6	11	9, 10	13	6
Total cases	3	3	4	3	13

*The figures indicate the case number in the text.

Cases were classified as mild if the result of the tourniquet test was negative throughout the illness, if edema was minimal or absent and if the pulse and blood pressure remained stable. Moderate cases were those in which the patients exhibited a positive reaction to the tourniquet test, slight clinical edema, tachycardia and toxic symptoms. The disease was considered severe if severe purpura, moderate to pronounced clinical edema, delirium and other signs of severe infection were present. Cases were classified as fatal whether death resulted directly from the infection itself, from a complication or as a result of unwisely selected therapy.

Method.—Studies were done serially in each case. The initial studies were done as soon as possible after the patient's admission to the hospital regardless of the duration of the infection; they were repeated at the clinical peak of the disease and during convalescence in the hospital. Whenever feasible, additional studies were done during the acute phase and after complete recovery from the disease.

3. The Pediatrics Service of the North Carolina Baptist Hospital and Physicians in the Sternberger Hospital, Greensboro, and in the Rowan Memorial Hospital, Salisbury, assisted in the clinical management of some of the patients.

The plasma volume was determined by the T-1824 dye (Evans blue) method as modified for the Evelyn photoelectric microcolorimeter.[4] Two cubic centimeters of a solution containing 3 mg. of the dye per cubic centimeter was injected, and at least three samples were taken at ten minute intervals on each patient; the first was obtained ten minutes after the injection of the solution. The standard value for each adult, indicated by the normal base line in the graphs, was calculated as 5 per cent of the body weight immediately prior to the onset of the illness. If the weight was unknown, the expected weight was calculated from height and age.[5] In children the plasma volume was calculated at 6 to 7 per cent of the body weight prior to the onset of illness, depending on the age.

The hematocrit value was determined on venous blood collected without stasis in bottles containing potassium and ammonium oxalate; the tubes were centrifuged for thirty minutes at 3,000 revolutions per minute. The standard hematocrit value was considered as 38 volumes per cent in females and 40 volumes per cent in males, regardless of age. The total blood volume was calculated from the hematocrit reading and the plasma volume. The total circulating red cell volume was calculated from the plasma and total blood volumes.

Determinations of the thiocyanate space were performed simultaneously with those of the plasma volume.[4] Eight cubic centimeters of a solution containing 50 mg. of sodium thiocyanate per cubic centimeter was injected with the dye; at least three blood samples were obtained at ten minute intervals. The standard thiocyanate fluid space was calculated as 20 per cent of the standard body weight in adults and as 25 to 30 per cent of the body weight in children, depending on the age of the patient. The scale on the graph was adjusted so that the standard falls opposite the horizontal base line.

In our hands, the values obtained from duplicate determinations of the plasma volume and the thiocyanate space on these patients and serial determinations on normal persons have not varied more than 10 per cent; therefore, only values which deviated more than 10 per cent from the standard base line for the patient were considered significant in the interpretation of data.

Chemical examinations of the blood were done by standard methods. The total serum protein contents were determined by the Kjeldahl, falling drop and copper sulfate specific gravity methods; usually at least two methods were employed each time as a check. The carbon dioxide—combining power and the blood levels of nonprotein nitrogen, chloride and para-aminobenzoic acid are not included in the data, although determinations of these were made in each case. The results of hematologic studies, which were done with certified pipets and counting chambers, are likewise omitted; the hemoglobin content was determined with the photoelectric colorimeter by the alkaline hematin method.

Results.—Because of the considerable variations in the severity of the disease, it is extremely difficult, if not impossible, to summarize the data. For that reason, brief case summaries are presented to illustrate the

4. Gregersen, M. I., and Stewart, J. D.: Simultaneous Determination of Plasma Volume with T-1824, and "Available Fluid" Volume with Sodium Thiocyanate, Am. J. Physiol. **125**:142-152 (Jan.) 1939. Gibson, J. G., and Evelyn, K. A.: Clinical Studies of the Blood Volume: IV. Adaptation of the Method to the Photoelectric Microcolorimeter, J. Clin. Investigation **17**:153-158 (March) 1938.

5. Duncan, G. G.: Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment, Philadelphia, W. B. Saunders Company, 1942, p. 935.

principles involved. The supportive therapy administered was based on the principles outlined in previous publications.[6] Specific therapy consisted of administration of para-aminobenzoic acid (PABA) or hyperimmune rabbit antiserum.[7] The latter was administered intramuscularly or intravenously in doses of 1 cc. per kilogram of body weight daily for a maximum of three days.[1] No serum was administered if the initial dose could not be given by the third day of rash. Para-aminobenzoic acid was administered by mouth or stomach tube on a two hour schedule day and night; the individual dose ranged from 0.5 to 2 Gm. per kilogram of body weight.

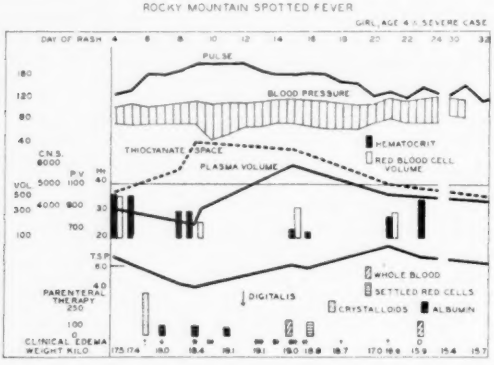

Fig. 1.—Severe Rocky Mountain spotted fever in a girl aged 4½.

SUMMARY OF CASES

CASE 1.—*Supportive therapy; typical severe case* (*fig.* 1).

Note the gradual rise in pulse rate and increase in thiocyanate space accompanied with a fall in diastolic blood pressure and in plasma volume and total serum protein content. After the administration of serum albumin, the plasma volume rose 6 cc. for every gram of albumin injected. With the increase in plasma volume and the return of capillary integrity, central (myocardial) circulatory failure, requiring the administration of digitalis, developed.

CASE 2.—*Supportive therapy; typical mild case* (*fig.* 2).

Note that the rise in pulse rate, drop in diastolic blood pressure and increase in thiocyanate space were minimal. The plasma volume rose with the development of immunity. The total serum protein content was never low, and no edema was

6. Harrell, G. T.; Wolff, W. A., and Venning, W.: A New Approach to Basic Supportive Therapy in Rocky Mountain Spotted Fever, South. M. J. **38**: 367-371 (June) 1945. Harrell, Wolff, Venning and Reinhart.[1] Harrell, Venning and Wolff.[2]

7. The hyperimmune rabbit antiserum was furnished by Lederle Laboratories, Pearl River, N. Y.

present. The changes are qualitatively the same as those in more severe cases but quantitatively much less marked.

CASE 3.—*Supportive therapy; fatal case; patient overloaded with crystalloids* (*fig.* 3).

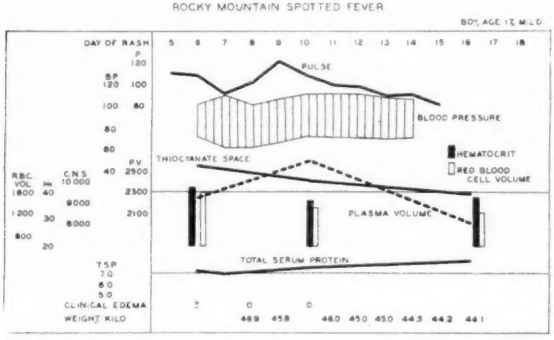

Fig. 2.—Mild Rocky Mountain spotted fever in a boy aged 17.

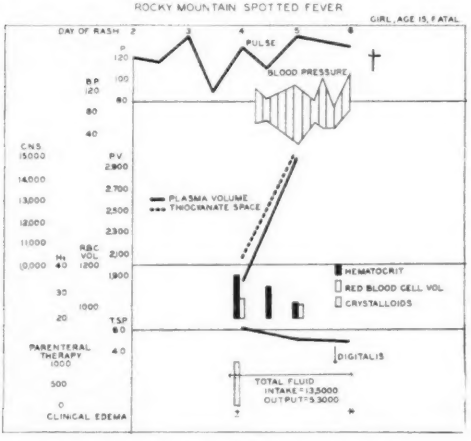

Fig. 3.—Fatal case involving a girl aged 15.

On the patient's admission to the hospital, the condition was classified as mild or moderately severe. The pulse rate was increased, but no change in blood pressure, plasma volume, thiocyanate space or serum proteins was found. Excessive amounts of crystalloids were administered orally to overcome dehydration. The pulse rate showed little change, but the diastolic blood pressure dropped, the plasma volume and the thiocyanate space increased markedly and the serum pro-

tein content fell slightly. The clinical picture of rapidly developing medullary edema with respiratory arrest resembled bulbar poliomyelitis; peripheral edema rapidly increased, and the patient died.

CASE 4.—*Supportive therapy; moderately severe case; unnecessary use of preformed protein* (*fig.* 4).

On admission to the hospital, the patient had a low serum protein content and edema, with a lowered diastolic blood pressure, but was not in shock. The plasma

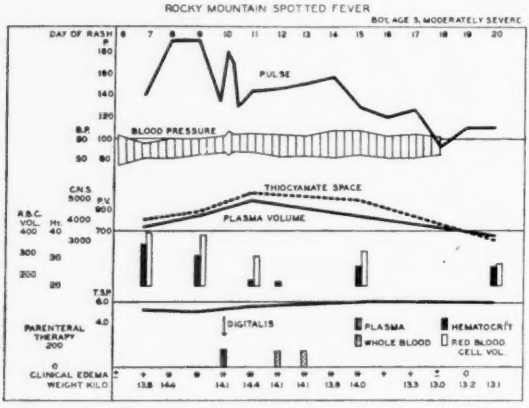

Fig. 4.—Moderately severe case involving a boy aged 3.

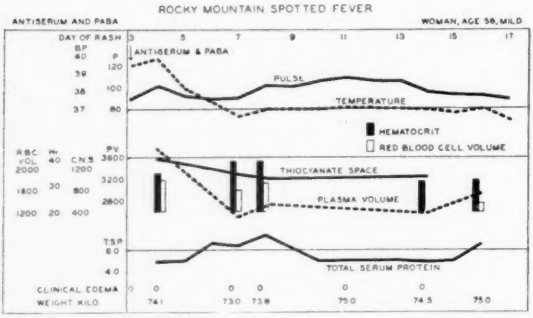

Fig. 5.—Effect of administration of antiserum and para-aminobenzoic acid in a woman, aged 56, with a mild form of the disease.

volume was not lowered, but the thiocyanate space was increased. The plasma volume was increasing as recovery began, and the pulse was dropping when plasma was administered. Gallop rhythm with central (myocardial) circulatory failure was precipitated. With rapid digitalization and a decrease in fluid intake, the abnormality was corrected.

CASE 5.—*Specific therapy with antiserum and para-aminobenzoic acid; mild case* (*fig.* 5).

The administration of both antiserum and para-aminobenzoic acid early in the course of the patient's mild illness did not prevent a drop in plasma volume. There was no increase in thiocyanate space, and edema did not develop. It was felt that the mildness of the infection was a greater factor in the prevention of edema, maintenance of serum proteins and failure of the thiocyanate space to increase than was the specific therapy.

CASE 6.—*Specific therapy with para-aminobenzoic acid; mild case* (*fig.* 6).

The patient presented an increased pulse rate, a lowered blood pressure, a lowered serum protein content and a slight increase in the thiocyanate space but no change in the plasma volume. The course was mild, and clinically he appeared

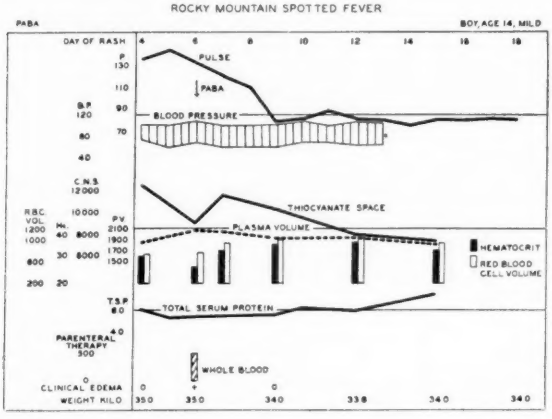

Fig. 6.—Effect of administration of para-aminobenzoic acid in a boy, aged 14, with a mild form of the disease.

to be recovering when specific therapy with para-aminobenzoic acid was initiated on the sixth day of rash. It was felt that the course of the mild infection was unaltered by the late administration of the drug.

CASE 7.—*Supportive therapy; mild case complicated by encephalitis* (*fig.* 7).

There was no change in plasma volume, thiocyanate space or serum protein content on the patient's admission to the hospital, though the pulse rate was increased and the blood pressure low. Because of encephalitis and coma, he was maintained on an inadequate oral protein intake (1 Gm. per kilogram of body weight daily), and an attempt was made to substitute protein hydrolysate by intravenous administration as a source of protein-building materials. Fifty grams of protein hydrolysate (1 Gm. per kilogram) was given daily. The failure of this therapy is shown by the fact that the thiocyanate space increased later than usual in the course of the disease, after capillary integrity had begun to be restored (as is illustrated by the increase in plasma volume). Gavage feedings were then begun (4 Gm. of protein per kilogram daily). The greater efficacy of preformed proteins in the form of whole blood, as compared with protein hydrol-

ysate, in raising the total serum protein content and decreasing edema is illustrated in the graph. Dehydration developed when parenteral therapy was discontinued, as is shown by the drop in thiocyanate space in the fourth week of rash.

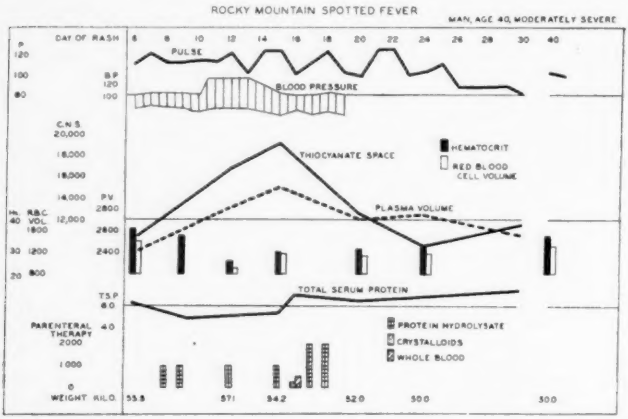

Fig. 7.—Moderately severe Rocky Mountain spotted fever in a man aged 40.

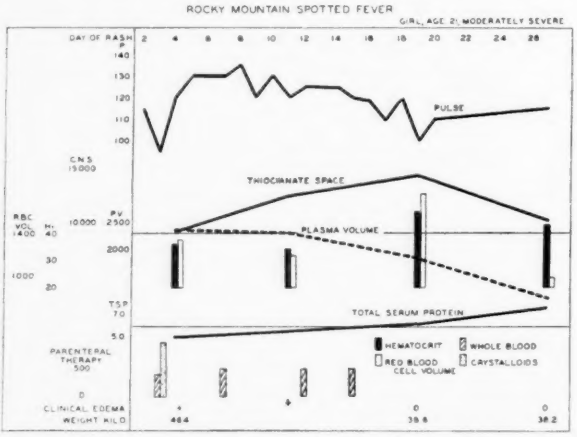

Fig. 8.—Moderately severe Rocky Mountain spotted fever in a woman aged 21.

CASE 8.—*Supportive therapy; moderately severe case in which there was an inadequate protein intake* (*fig.* 8).

Early in the course of the patient's illness there was no change in the thiocyanate space or the plasma volume, though the pulse rate was increased and

the serum proteins were low. The patient ate little and did not tolerate a gavage tube. The inadequacy of the usual quantity of preformed proteins as the sole source of protein intake is illustrated by the late increase in the thiocyanate space and the drop in plasma volume after capillary integrity should have been restored. The rise in serum protein content and in the hematocrit value toward the end of the hospital stay indicates the necessity for repeated transfusions in such instances. Asthenia was present to a notable degree throughout the entire course of the disease and continued for weeks into convalescence.

CASE 9.—*Specific therapy; severe disease treated with antiserum and para-aminobenzoic acid (fig. 9).*[8]

The patient was severely ill on admission to the hospital. The pulse rate was increased, the blood pressure low and the thiocyanate space increased; the plasma volume and the serum protein content were not altered. With hydration, the thio-

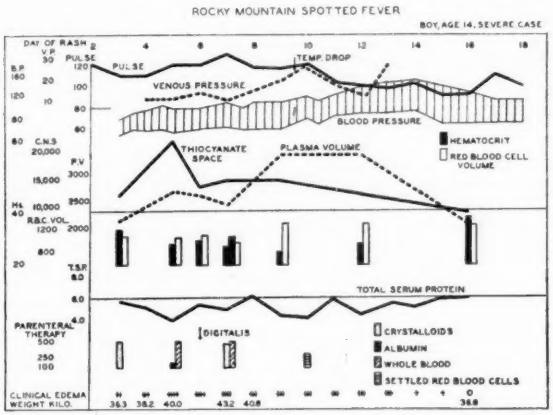

Fig. 9.—Severe case involving a boy aged 14.

cyanate space increased and the serum protein content dropped simultaneously with the development of notable clinical edema. The administration of antiserum from the third to the sixth day of rash caused little improvement. Administration of para-aminobenzoic acid was then started; the peak blood levels were attained between the ninth and eleventh days of rash, when clinical recovery usually begins. With the rise in plasma volume, central circulatory failure developed and was controlled with digitalis. As convalescense progressed, the blood pressure rose, the pulse rate dropped and the plasma volume, thiocyanate space and serum protein content returned to normal. A high oral protein intake (approximately 5 Gm. per kilogram of body weight daily) was maintained. Anti-histaminic drugs were administered but not until the twenty-second day of the rash, after the circulatory

8. This case is reported in greater detail in the American Practitioner **1**:425-435 (April) 1947. Photographs of the patient and colored diagrams illustrating the mechanism by which circulatory failure can be precipitated through unwisely chosen parenteral therapy are included.

changes had reverted to normal. The necessity for meticulous attention to every minor detail of supportive therapy is well illustrated; it was the unanimous opinion of all the physicians up until the tenth day of rash that the patient would die.

CASE 10.—*Specific therapy; patient with severe disease treated with para-aminobenzoic acid* (*fig.* 10).[9]

The patient was severely ill when first seen by us. The blood pressure was lowered, the thiocyanate space increased and the serum protein content low although the plasma volume was normal. In spite of vigorous supportive therapy and massive doses of para-aminobenzoic acid, circulatory collapse developed; it was corrected by the administration of albumin. With the return of capillary integrity, the thiocyanate space decreased and the plasma volume and serum protein content rose; central circulatory failure developed and was controlled by digitalis. The failure of para-aminobenzoic acid to maintain capillary integrity in severe as well as in mild cases is illustrated.

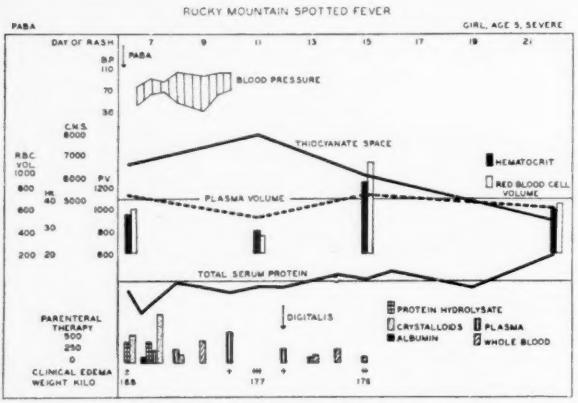

Fig. 10—Effect of administration of para-aminobenzoic acid in a girl, aged 5, with a severe form of the disease.

CASE 11.—*Specific therapy; patient with moderately severe disease treated with antiserum; the reproduction of the physiologic changes of spotted fever during serum sickness* (*fig.* 11).

The patient showed signs of dehydration and toxemia on admission to the hospital. The administration of antiserum decreased the toxic symptoms but did not prevent the alterations in capillary permeability. The thiocyanate space increased, the plasma volume and the serum protein content dropped and edema developed. With the restoration of capillary integrity during clinical recovery (manifested by the drop in temperature and the decrease in toxic symptoms), the edema disappeared and the thiocyanate space decreased but the plasma volume

9. This case was reported in greater detail in regard to the effect of para-aminobenzoic acid by S. F. Ravenel (Para-Aminobenzoic Acid Therapy of Rocky Mountain Spotted Fever: Outline of Comprehensive Plans of Treatment with Report of Five Cases, [case 5], J.A.M.A. **133**:989 [April 5] 1947).

remained low. When serum sickness developed, edema returned and the thiocyanate space increased markedly but the plasma volume and serum protein content showed little change. Benadryl(R) (beta dimethylaminoethyl benzhydryl ether hydrochloride) was given. After recovery from serum sickness and the disappearance of edema, the thiocyanate space, plasma volume and serum protein content all decreased.

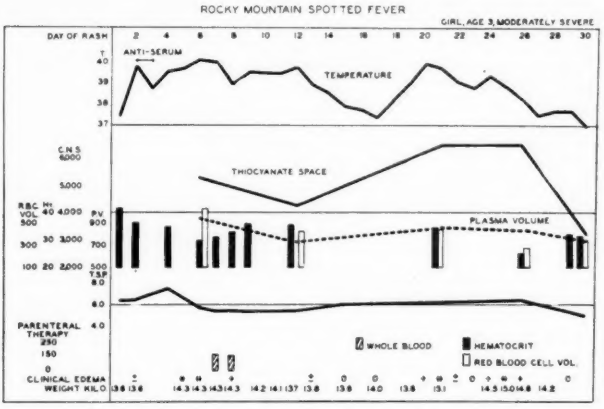

Fig. 11.—Moderately severe Rocky Mountain spotted fever in a girl aged 3

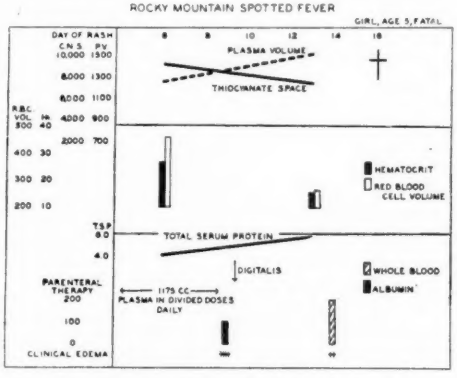

Fig. 12.—Fatal case involving a girl aged 5.

CASE 12.—*Specific therapy with para-aminobenzoic acid; fatal case complicated by pneumonia and myocardial failure* (*fig.* 12).

The patient was severely ill from the beginning. The oral protein intake was low, and an attempt was made to compensate for this deficiency by multiple in-

fusions of plasma. The thiocyanate space remained high and the serum protein content low, though the plasma volume was maintained in spite of considerable edema. The administration of serum albumin precipitated myocardial failure, which was only partially controlled with digitalis. Lobar pneumonia developed and did not respond to penicillin therapy. Terminally pulmonary edema was present as well. The administration of para-aminobenzoic acid did not prevent the alteration of capillary permeability to crystalloids.

CASE 13.—*Specific therapy with antiserum and para-aminobenzoic acid; fatal case complicated by massive intestinal hemorrhage* (*fig.* 13).

The patient was moderately ill on admission to the hospital. The pulse rate was not increased, and the plasma volume was normal; the thiocyanate space was increased, though no clinical edema was present. Antiserum was administered, but it did not change the character or decrease the rate of spread of the rash. The rise

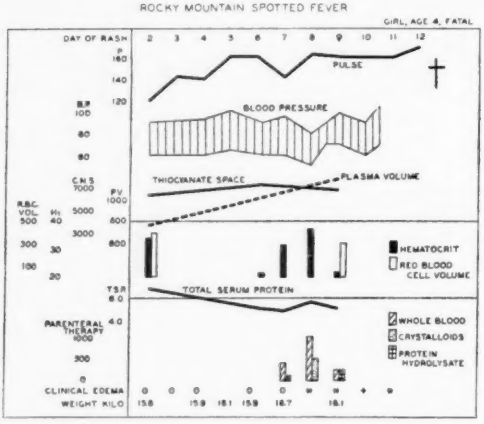

Fig. 13.—Fatal case involving a girl aged 4.

in pulse rate and the drop in blood pressure were due to bleeding from the bowel. At first the plasma volume was unaltered, but in the seventh day of rash the patient was in shock; almost the entire circulating blood volume was replaced intravenously in less than twelve hours, and the blood pressure and the serum protein content rose. Para-aminobenzoic acid was administered late in the course, without producing any alteration in the clinical picture. Clinical edema developed, although there was no decided change in the thiocyanate space. At autopsy, lesions of the small blood vessels resembling periarteritis nodosa were seen in many organs.

From these data several generalizations can be made. Early in the course of the disease, dehydration and lowering of the blood chloride content are common; the dehydration is accompanied with little change in the plasma volume and thiocyanate space unless crystalloids are administered in large quantities. Capillary permeability to crystalloids, protein and red blood cells is altered progressively as the disease increases

in severity. The alteration is greatest near the clinical peak of the disease, between the tenth and fourteenth days of rash; at this time there is a tendency for the plasma volume and the serum protein content to drop, the thiocyanate space to increase and clinical edema to develop. These alterations can be accelerated by the excessive administration of crystalloids alone. The alteration in capillary permeability is corrected with clinical recovery, which is evidenced by a drop in temperature and a decrease in toxic symptoms.

Under the conditions of these experiments the administration of hyperimmune rabbit antiserum and para-aminobenzoic acid (PABA) did not prevent the alteration in capillary permeability to crystalloids. The data suggest that some decrease in the permeability of capillaries to protein may occur under therapy with para-aminobenzoic acid.

COMMENT

Relation of Capillary and Cellular Permeability to Immunity.—An increase in the capillary permeability occurs in the course of Rocky Mountain spotted fever; the alteration can be detected early in the course of the disease but is most significant during the second week of rash—the time at which immunity and allergy may be expected to develop. Allergy has not been demonstrated in rickettsial diseases, however. That an immune mechanism is involved in the alteration of capillary permeability is suggested by the similarity of the changes observed during serum sickness (case 11) to those observed during the course of rickettsial spotted fever.

It has been known for years that antigen-antibody reactions liberate a histamine-like substance. That histamine and similar substances alter capillary permeability is demonstrated by the production of a wheal when histamine is injected into the skin. In Rocky Mountain spotted fever the maximum changes in capillary permeability occur at the time when immunity is rising rapidly and is beginning to attain ascendency over the infection. Our observations in cases of Rocky Mountain spotted fever suggest that the antigen-antibody effect involves the general circulation and alters the permeability of the entire vascular tree.

Because rickettsias are located intracellularly, one would expect cellular as well as capillary permeability to be increased. The fact that cells participate in the immune process and are affected by allergic manifestations is well known. An antigen-antibody reaction occurring within the cell might be expected to liberate a histamine-like substance which would increase the permeability of the cell membrane. In patients with spotted fever it is difficult to obtain an adequate quantity of interstitial fluid for chemical examination by the insertion of needles subcutaneously. In view of the ease with which fluid can be obtained from patients with

congestive failure, we are led to suspect that some of the fluid lost from the circulation in spotted fever may be found within cells as well as between them. The disproportion between the changes in weight and the changes in thiocyanate space also suggests that cellular hydration occurs. The observation of stupor, tremor and medullary respiratory arrest (case 3) is clinical evidence that nerve cells are hydrated excessively; the increase in cerebrospinal fluid pressure in such instances is usually less than would be expected if the cerebral edema were interstitial.

Unfortunately, no technic is available at present for the measurement of intracellular fluid. Regardless of whether the fluid goes into tissue space or into cells, the loss from the circulating intravascular fluid lowers the blood volume and precipitates peripheral circulatory collapse.

Since the effect on permeability of membranes is not confined to the cells but presumably affects the capillary wall between cells, one might postulate that at least one antigen involved in the immune reaction is a soluble one. If this hypothesis is correct, the substance produced by the rickettsias inside cells would diffuse out and induce an antibody response in the circulation. Thus, humoral as well as cellular immunity would develop, and antigen-antibody reactions would occur in the circulation on the surface of cells and within them.

In any event, the alterations in permeability are evidently reparable with the establishment of immunity; this conclusion is based on clinical observation alone, however, since no quantitative data on the degree of immune response were obtained. The diuresis which regularly occurs with recovery from infectious diseases has been known to clinicians for years, though the mechanism has never been explained.[10] The restoration of capillary and cellular integrity would enable interstitial and intracellular fluid to be mobilized and excreted through the kidney.

The Similarity of Serum Sickness to Rocky Mountain Spotted Fever.—The observations made in case 11 during the patient's serum sickness led to further experimental studies, which are being reported separately.[11] Serum sickness produced in rabbits by the administration of human plasma caused the increase in thiocyanate space, drop in circulating plasma volume, drop in serum protein content and development of edema seen in cases of Rocky Mountain spotted fever. The recent introduction of antihistaminic drugs raises the interesting possibility of preventing the harmful effects of immune reactions without affecting the

10. Rackemann, F. M.; Longcope, W. T., and Peters, J. P.: The Excretion of Chlorids and Water and the Renal Function in Serum Disease, Arch. Int. Med. **18**:496-504 (Oct.) 1916.

11. Aikawa, J. K.: The Immuno-Physiology of Serum Sickness: Alterations in the Blood Volume and Thiocyanate Space in Relation to the Development of Immunity, to be published.

beneficial ones. The administration of antihistaminic drugs, "benadryl" and "pyribenzamine," in cases 9 and 11 was too late in the course of the disease to enable us to draw definite conclusions. The favorable response following the administration of these drugs to patients with serum sickness suggests that a beneficial effect might be achieved.

The Effect of Therapy on Permeability and Circulatory Failure.—The administration of supportive therapy alone to 7 patients did not prevent the development of circulatory failure in some cases. The necessity for the administration of large amounts of protein to replenish or conserve protein stores and to maintain the circulating plasma and blood volume is well illustrated in cases 7, 8 and 10.

A few observations on the response of the blood volume to the administration of serum albumin (as in case 1) indicate that the rise in the plasma volume was less than would be expected from the experience in other diseases. Usually an increase of 14 cc. for each gram of albumin injected may be anticipated.[12] When this increase does not occur, it is not known whether the albumin is stored or leaks into tissue spaces.

Since immune bodies are found in the globulin fraction of serum, the chance presence of immune bodies to rickettsias might explain the reactions to transfusions of blood and plasma observed occasionally in patients with Rocky Mountain spotted fever.[13] If this explanation is correct, serum albumin should be used to support the circulation when preformed protein is necessary in the treatment of circulatory collapse; if the hematocrit value is low and anemia is simultaneously present, settled or washed red cells should be used in preference to whole blood. Because of the large amounts of plasma necessary to maintain the circulating blood proteins in the face of the pronounced degree of protein destruction and nitrogen excretion observed in the disease, every effort should be made to encourage maintenance of protein stores by feeding rather than by replacement with transfusion.[1]

The administration of specific therapy to 6 patients either early or late in the course of the disease did not prevent the development of peripheral circulatory failure. No evidence was found that the doses of antiserum used raised the antibody titer sufficiently to increase the permeability of membranes; in all likelihood the immune balance was not shifted with this quantity of antibody. Since the rickettsias require several days to become established intracellularly, one would anticipate

12. Cohn, E. J.; Oncley, J. L.; Strong, L. E.; Hughes, W. L., Jr., and Armstrong, S. H., Jr.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: I. The Characterization of the Protein Fractions of Human Plasma, J. Clin. Investigation **23**:417-432 (July) 1944.

13. Martin D. W.: Rocky Mountain Spotted Fever in Children, J. Pediat. **16**:468-472 (April) 1940.

that the early administration of adequate quantities of serum might decrease or prevent the parasitization of cells and the subsequent alteration in the permeability of cellular membranes; prevention of an increase in capillary permeability would not necessarily be expected.

The administration of para-aminobenzoic acid early or late in the course of the disease did not prevent circulatory failure. The recurrence of an increase in thiocyanate space without a simultaneous drop in plasma volume in the patients in cases 6 and 12 while they were under therapy with para-aminobenzoic acid suggests that this drug may decrease the extent of capillary permeability so that only slightly increased amounts of crystalloids and no proteins are passed by the capillary membrane. If this hypothesis be true, administration of para-aminobenzoic acid would exert its effect through interference with the product of an antigen-antibody reaction and hence could be classed as supportive rather than specific therapy. This drug is chemically similar to salicylates and procaine, both of which have been used to alleviate the symptoms of serum sickness.

Pathogenesis of Central (Myocardial) Circulatory Failure.—In some instances, such as cases 9 and 10, myocardial failure as well as peripheral circulatory collapse was observed. In other instances (cases 1 and 4) congestive failure was precipitated by therapy. Changes in the electrocardiogram on all patients with spotted fever were not observed, and few electrocardiographic readings have been made during the acute episodes of congestive failure. The changes in the electrocardiogram observed in previous cases are similar to those which occur with edema due to beriberi, myxedema or anasarca of other cause. Pathologically, sections of the myocardium in fatal cases usually show edema of the muscle fibers. In other fatal cases, lesions resembling periarteritis nodosa have been seen in small blood vessels, as in case 13. Two mechanisms may be involved in the myocardial failure, i.e., mechanical interference from edema and anoxia from the involvement of arterioles.

SUMMARY

1. Peripheral circulatory failure in rickettsial spotted fever is accompanied with a drop in serum protein content and the development of edema.

2. The plasma volume is decreased and the thiocyanate space increased in the second week of the disease, when circulatory changes are at a maximum.

3. With the establishment of immunity (or allergy), capillary integrity is restored, diuresis occurs, the edema disappears, the plasma volume increases and the patient recovers.

4. The fact that the circulatory changes are at a maximum during the second week of the disease, when immunity begins to attain ascendency over the infection, suggests that an antigen-antibody reaction may be responsible for the changes in permeability of the membranes.

5. An alteration in the permeability of membranes was observed in 1 patient during serum sickness induced by the therapeutic administration of Rocky Mountain spotted fever antiserum; the changes resembled those seen during the rickettsial infection and give support to the aforementioned hypothesis.

6. An alteration of permeability probably takes place in cell membranes as well as in capillary walls; the capillary permeability may progressively increase in degree, so that crystalloids, protein and red blood cells are allowed to pass out of the capillaries.

7. Myocardial failure may occur as the direct result of the anoxia induced by vascular lesions of the disease or by interstitial edema, or it may be precipitated by excessive administration of fluids, particularly during the period when capillary integrity is being restored.

8. In 6 cases specific therapy in the form of antiserum or para-aminobenzoic acid, alone or together, early or late in the course of the disease did not prevent circulatory changes.

9. Supportive therapy does not prevent the circulatory changes of spotted fever, but a high protein diet administered from the beginning of therapy reduces the physiologic effects of the disease; serum albumin is probably the best preformed protein for parenteral administration in cases of acute circulatory collapse.

10. In other infectious diseases in which the permeability of membranes may be altered, proper replacement of protein and the avoidance of excessive administration of crystalloids might decrease circulatory failure; the principles of supportive therapy described are probably applicable to these infectious diseases.

SURGICAL TREATMENT FOR HYPERTENSIVE COMPLICATIONS OF ADVANCED RENAL DISEASE

EDWARD C. PERSIKE, M.D.
RICHARD W. LIPPMAN, M.D.
T. ADDIS, M.D.
FREDERICK L. REICHERT, M.D.
AND
VICTOR RICHARDS, M.D.
SAN FRANCISCO

MANY AUTHORS consider uremia due to bilateral renal disease in its terminal stages as a contraindication to splanchnicectomy and sympathectomy.[1] Patients with this condition are supposed to be inferior operative risks, and their chances of survival for more than a few years presumably are small. When medical measures fail, however, these fears should not prevail if relief can be obtained from agonizing headaches and loss of functional vision and if it can be shown that the operation can be performed with reasonable safety.

A bilateral splanchnicectomy and sympathectomy was performed in one stage by two operative teams on each of 10 patients with glomerular nephritis in the terminal stage. Their ages varied from 25 years to 36 years. All suffered from renal failure, with serum creatinine concentrations ranging from 2.22 to 8.75 mg. per hundred cubic centimeters. Their preoperative blood pressures averaged 235 systolic and 150 diastolic, the lowest being 184 systolic and 134 diastolic and the highest 290 systolic and 185 diastolic. Eight patients complained of severe headaches which

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From the departments of medicine and surgery, Stanford University School of Medicine.

1. (*a*) Peet, M. M.: Hypertension and Its Surgical Treatment by Bilateral Supradiaphragmatic Splanchnicectomy, Am. J. Surg. **75**:48 (Jan.) 1948. (*b*) Woods, W. W.: The Surgical Treatment of Hypertension: Results of Clinical and Experimental Investigations, J. Urol. **48**:16 (July) 1942. (*c*) Craig, W. M., and Adson, A. W.: Hypertension and Subdiaphragmatic Sympathetic Denervation, S. Clin. North America **19**:969 (Aug.) 1939. (*d*) Smithwick, R. H.: The Surgical Treatment of Hypertension: Some Circumstances Under Which Lumbodorsal Splanchnicectomy Appears to Be Inadvisable in Hypertensive Patients, New York State J. Med. **44**:2693 (Dec. 15) 1944. (*e*) Grimson, K. S.: The Surgical Treatment of Hypertension, in Dock, W., and Snapper, I.: Advances in Internal Medicine, New York, Interscience Publishers, 1947, vol. 2, p. 173.

did not respond to medical treatment, and 9 patients experienced loss of functional vision. All the patients had advanced retinal changes, with hemorrhages and exudates, and papilledema was present in 5. One patient died during the immediate postoperative period, and it was not possible to follow 2 patients after operation. The postoperative changes which occurred in the remaining 7 patients and their postoperative management are the subjects of this paper.

SELECTION OF PATIENTS FOR OPERATION

Hypertensive complications in patients with glomerular nephritis usually do not appear after the brief initial stage until the terminal stage when azotemia is present. In these circumstances attempts to lower the blood pressure by rigid restriction of salt may precipitate symptoms of severe salt depletion because diminished tubular function depresses the reabsorption of sodium. In such cases we have been reluctant to prescribe less than 5 Gm. of sodium chloride daily, unless the urinary excretion of sodium chloride falls below this figure and the patient simultaneously gains weight.

Hypertensive headaches sometimes are prevented or diminished in intensity when the patient's head is elevated during the sleeping hours. The severity of these headaches sometimes will decrease after a period of rest and reduced activity. Occasionally, the institution of an adequate low protein diet (0.5 Gm. of protein per kilogram of body weight plus an increment equal to the amount of protein excreted in the urine) will alleviate symptoms and lower the blood pressures of patients whose consumption of protein in food previously had been unrestricted.[2]

We have been reluctant to recommend operation until both the patient and the physicians feel driven to seek any possible benefit from surgical intervention. Despite the most careful medical management, certain patients will become disabled and intolerably miserable as a consequence of progression in their hypertensive complications. These are the patients who have been selected for operation.

OPERATION

Bilateral paravertebral incisions are made by two surgeons working as a team, and the operation is carried on simultaneously on both sides. The long back musculature is divided, and segments of the eleventh and twelfth ribs are resected from the transverse processes laterally for 3 to 4 cm. The pleura is pushed away from the vertebral bodies. The

2. Lippman, R. W., and Persike, E. C.: Ambulatory Management of Azotemia and Clinical Uremia, Arch. Int. Med. 80:579 (Nov.) 1947.

outer crus of the diaphragm is pushed off or separated from the body of the first lumbar vertebra. The retropleural and upper retroperitoneal areas are thereby exposed, which permits palpation of the kidneys and adrenal glands. The sympathetic chain is resected from the eighth or ninth thoracic ganglion down to and including the first lumbar and usually the second lumbar ganglion. The greater and lesser splanchnic nerves are resected from the eighth or ninth thoracic ganglion down to and including the upper half of the celiac ganglion. Ordinarily, the patient receives 500 cc. of whole blood during the operation, and neosynephrine hydrochloride[R] is administered by the anesthetist as is necessary after the sympathectomy, 0.1 cc. of a 1:1,000 solution being used intravenously.

POSTOPERATIVE CARE

The blood pressure may fall precipitously to dangerous levels during and after a one stage splanchnicectomy and sympathectomy if special efforts to maintain it are not employed. Shock, cerebral anoxia and renal ischemia are the principal dangers, the last complication being of particular importance in patients with advanced renal disease. The one postoperative fatality in this group of patients occurred from cerebral anoxia and symmetric necrosis of the renal cortexes after an eight hour fall in blood pressure from bleeding at the operative site. Administration of whole blood during the operation helps to maintain the blood pressure and aids in compensating for operative blood loss and postoperative oozing.[3] All the patients in this series were anemic from renal failure preoperatively, but no particular benefit was noted from the use of transfusion before operation except when the anemia was severe. Measurements of blood pressure should be made every five to fifteen minutes during the first postoperative day and as frequently thereafter as is indicated. If the blood pressure falls below 150 systolic and 100 diastolic, neosynephrine hydrochloride[R] should be administered intravenously. It may be necessary at times to infuse the drug, diluted with 5 per cent dextrose in distilled water, continuously.

Maintenance of an adequate fluid balance in patients with advanced renal disease and azotemia is of the utmost importance. If dehydration and salt depletion occur, it may be difficult to sustain the blood pressure at desired levels, the azotemia may be intensified and acidosis may ensue. Administration of excess salt and water may result in edema and in heart failure. Estimation of the optimum quantities of salt and water to be given may be difficult because of hypotension, pro-

3. Lord, J. W., and Hinton, J. W.: The Operative and Postoperative Management of Hypertensive Patients Undergoing Thoracolumbar Sympathectomy, New England J. Med. **237**:840 (Dec. 4) 1947.

fuse postoperative diaphoresis and anuria or oliguria, which commonly occurs during the first twenty-four to forty-eight postoperative hours.

Twenty-four hour specimens of urine should be collected throughout the period of hospitalization. The volume of urine and the quantity of sodium chloride excreted should be measured daily. The total fluid intake and output should be measured and charted. The initial postoperative period of anuria or oliguria presents a particular problem. Fluids should be given slowly and cautiously but in a sufficient quantity to maintain hydration and to replace loss from sweating, respiratory exchange, vomiting and bleeding. The necessary quantity usually is about 2,000 cc. daily in excess of that lost by vomiting. Since little or no salt is lost in the urine, only enough to replace that lost by sweating and vomiting is needed. When urine again is secreted freely, daily excretory rates of 3,000 cc. of urine and 5 Gm. of sodium chloride are probably optimum.

Unless an adequate number of calories is supplied, body protein will be used for energy, deamination of amino acids will be increased and the azotemia may be intensified. Solutions given intravenously should contain dextrose in concentrations of 5 or 10 per cent, and the patient should be urged to consume food and fruit juices with sugar as early as possible after operation. When food can be eaten without difficulty, an adequate low protein diet should be given. Intravenous or oral administration of protein or amino acid preparations should be avoided, for protein in excess of anabolic needs imposes added work on the kidneys[4] and may increase the concentrations of nitrogenous metabolites in the blood.

Seconal and pentobarbital sodium (nembutal^{R}) are preferred for sedation because they are detoxified principally in the liver. Barbital, phenobarbital and other barbiturates which depend on the kidneys for elimination from the body may accumulate in patients with renal failure, causing depression and intoxication.[5]

RESULTS OF OPERATION

Blood Pressure.—The blood pressure dropped postoperatively in all the patients and became stabilized between 150 systolic and 100 diastolic and 180 systolic and 120 diastolic within two weeks after operation. These levels were maintained for two to eight months, after which the blood pressures slowly increased and again stabilized at new higher

4. Addis, T.: The Treatment of Chronic Renal Insufficiency, J. Urol. **41**:126 (Feb.) 1939; Glomerular Nephritis, New York, The Macmillan Company 1948.

5. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941.

levels, not particularly different from those which obtained before operation (table 1).

Headache.—The patients who suffered from headaches were completely relieved of this symptom immediately after operation. Headaches returned, but with diminished intensity, in 2 patients after five and eight months. The other 4 patients, followed for three to forty-nine months, have not experienced significant headaches since operation.

Loss of Functional Vision.—In every case vision returned to approximately normal within four to eight weeks after operation. The patients have been followed for three to forty-nine months, and in none has loss of functional vision recurred. Postoperative funduscopic

TABLE 1.—*Postoperative Changes in Blood Pressure*

Patient	Preoperative Blood Pressure	Blood Pressure Two Weeks Post-operatively	Blood Pressure One to Two Months Post-operatively	Last Post-operative Blood Pressure	Months
G.B.	240/140	140/100	160/100	220/130	11
K.S.	240/150	150/110	170/105	220/120	7
R.M.	250/150	128/90	145/105	220/160	9
J.D.	184/134	140/100	140/105	170/130	12
R.V.	290/185	150/100	145/105	165/115	3
B.M.	230/140		200/120	230/138	6
V.B.	250/150		160/110	210/145	49

examinations revealed a rapid reversal of the severe and progressive changes noted before operation. Structural abnormalities in the vessels and retinas did not regress, but retinal pallor decreased, papilledema quickly subsided and no further hemorrhages occurred. These observations are similar to those which have been described by others.[6]

Azotemia, Proteinuria and Renal Function.—After the first postoperative week, no changes ascribable to the operation regularly were noted in the serum concentrations of creatinine (table 2) or in the rates of urinary excretion of protein, erythrocytes, white blood cells, epithelial cells or casts, with one exception. This patient (J. D., table 2) was not given enough fluid, salt and calories during the first two postoperative days, during which time he became dehydrated and more

6. Peet, M. M., and Isberg, E. M.: The Surgical Treatment of Arterial Hypertension, J. A. M. A. **130**:467 (Feb. 23) 1946. Peet.[1a] Woods.[1b]

deeply uremic. His period of oliguria lasted for several days, and he appeared to be moribund. Corrective therapy with fluid, salt and calories, however, effected a gradual improvement. He has survived for twelve months since operation, but his serum creatinine concentration is still higher than its preoperative level.

Endogenous creatinine clearances, measured in 3 patients, were unaffected by the operative procedure. Foa and his associates[7] used inulin and diodrast[R] clearances to measure the effective renal blood flow in 17 hypertensive patients before and after splanchnicectomy and sympathectomy. The renal blood flow did not change, even when the blood pressure decreased after operation. Goldring and Chasis[8] also found no alteration in renal blood flow postoperatively.

TABLE 2.—*Serum Creatinine Concentrations (Milligrams per Hundred Cubic Centimeters)*

Patient	Preoperative Concentration	Concentration One to Two Months Postoperatively
R.M.	2.25	2.50
V.B.	2.96	2.69
R.V.	3.50	2.75
G.B.	3.75	3.50
K.S.	5.00	5.10
B.M.	6.68	5.77
J.D.	6.85	10.00

Capacity for Work.—All the paients were unable to pursue their regular occupations before operation because of the severity of their symptoms. Each patient who has been followed for three months or more returned to useful endeavor. One of these patients died after six months, and another died after ten months. The rest, however, have continued their work for periods up to forty-nine months.

7. Foa, P. P.; Woods, W. W.; Peet, M. M., and Foa, N. L.: Effective Renal Blood Flow, Glomerular Filtration Rate and Tubular Excretory Mass in Arterial Hypertension: II. Effect of Supradiaphragmatic Splanchnicectomy with Lower Dorsal Sympathetic Ganglionectomy, Arch. Int. Med. **71**:357 (March) 1943.

8. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease, New York, The Commonwealth Fund, 1944.

COMMENT

The benefits derived from operation by the patients of this group were worth while, even though their blood pressures were not reduced for long. Relief from incapacity and intolerable symptoms regularly occurred, and they were aided to lead useful lives. Two patients died from uremia after five months and eight months of freedom from their severe preoperative symptoms. The other patients have remained asymptomatic for periods ranging from three to forty-nine months.

Because of these observations, we do not consider advanced renal disease with azotemia as a contraindication to bilateral splanchnicectomy and sympathectomy. When medical treatment fails to alleviate severe hypertensive headaches or loss of functional vision and when symptoms become disabling, the patient should not be denied the good chance for symptomatic relief which the operation offers, even though he may be deeply uremic.

SUMMARY

Bilateral splanchnicectomy and lumbodorsal sympathectomy is not contraindicated in patients with advanced renal disease and azotemia. The operation is an effective remedy, affording symptomatic relief when hypertensive complications in these patients fail to improve with medical management and when the symptoms become unbearable and incapacitating.

ANTHROPATHOLOGY OF ARTERIAL TENSION

B. H. KEAN, M.D.
AND
JOHN F. HAMMILL, M.D.
NEW YORK

MOST physicians believe that there is a progressive rise of the arterial tension in normal persons from adolescence to old age. This is expressed by the familiar formula that normal systolic blood pressure should be 100 mm. of mercury plus the age of the individual. The figures compiled by Symonds[1] from over 100,000 life insurance applicants (table) indicated a progressive rise of blood pressure from 123.5 mm. of mercury systolic and 79.5 mm. diastolic in the age group 15 to 20 years to 135.2 mm. systolic and 86.9 mm. diastolic in the age group above 60 years. A slight to moderate increase of blood pressure above the popular normal has become of less and less concern.

In a recent study, Masters, Marks and Dack[2] advocated raising the normal scale of systolic blood pressure into the 140 mm. to 150 mm. range. One of their main reasons for advocating this elevation was the frequency with which such systolic levels were found in apparently normal persons. On the other hand, Robinson and Brucer[3] insisted that the standard of normal blood pressure be lowered. They stated the belief that so-called average blood pressures are much higher than normal because the blood pressures of patients with early hypertension are included so frequently that they weight the arithmetic average to an unduly high level. Here, then, are two schools of thought that are completely divergent.

Some years ago one of us (B.H.K.) was impressed by the enormous difference in the incidence of hypertension in two groups of people living and working side by side in Panama.[4] It was felt that a study of the blood pressure of primitive peoples might provide answers to the following questions:

From the Department of Pathology, Post-Graduate University, New York University, Bellevue Hospital Medical Center.

Anthropathology is a term used by Lewis (Lewis, J. H.: The Biology of the Negro, Chicago, University of Chicago Press, 1942, P. X.) to mean comparative racial pathology.

Blood Pressures of Various Races

Race	Country	Observers	Year	Number of Cases		Age, Years 15-20	20-25	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70	Over 70	Comment
.....	United States	Symonds [1]	1923	150,419	Average systolic	123.5	124.2	124.5	125.1	125.3	126.4	128.2	130.2	133.5	135.2	(60 years plus)		Insurance data
					Average diastolic	79.5	80.5	81.5	82.3	83.3	84.0	84.7	85.9	86.8	86.9	(60 years plus)		Insurance data
.....	United States	Robinson and Brucer [2]	1929	7,453 men	Average systolic	118.3	119.0	118.5	117.5	117.6	120.1	122.7	125.6	129.6	131.7	138.6	137.2	
					Average diastolic	68.2	70.8	72.0	72.7	74.0	75.7	77.0	77.3	78.2	77.5	76.7	77.3	
					% systolic 140 plus	3.1	5.6	4.8	4.6	5.1	9.2	1.5	2.2	25.4	29.1	43.9	43.8	
					% diastolic 90 plus	1.0	2.0	3.1	3.4	5.0	8.0	11.9	12.8	13.9	11.1	16.4	12.5	
				3,403 women	Average systolic	107.4	108.4	110.2	111.6	114.4	119.0	125.4	125.8	138.2	142.8	145.9	136.9	
					Average diastolic	63.9	65.4	67.1	69.0	70.7	73.2	75.4	75.7	79.0	81.0	80.2	75.0	
					% systolic 140 plus	0	0	1.5	1.8	5.4	12.3	20.9	21.4	37.6	46.5	57.2	71.4	
					% diastolic 90 plus	0	0	0.9	3.0	5.1	9.1	11.5	10.9	19.9	22.5	20.0	12.5	
.....	United States	Masters, Marks and Dack [3]	1943	8,000 men	Blood pressure of 140/90 or over		(1) All groups				33.6%		49.2%		66.5%		77.1%	
							(2) Industry				32.1%		44.9%		62.4%		81.1%	
					Blood pressure of 150/100 or over		(1) All groups				15.4%		31.7%		50.4%		61.3%	
							(2) Industry				14.8%		27.6%		31.8%		56.6%	
Primitive natives of Africa	Kenya Colony, Africa	Donnison [5]	1929	1,000	Average systolic	123.0	122.7	126.4	126.0	125.5	118.3	113.1	109.7	106.5		105.7		Ages of natives were estimated since they lacked accurate knowledge of own age
					Average diastolic	81.8	79.9	83.9	84.7	85.9	81.3	75.5	74.0	69.6		66.9		
African negroes	Uganda, Africa	Williams [6]	1941	A 394	Average systolic	120		124		126		127		127				A—all men
					Average diastolic	74		78		79		79		75				
				B 356	Average systolic			121		120.9								B—men and women
					Average diastolic			75.5		75.5								
Aborigines of Australia	Australia	Hicks and Matters [7]	1933	46	Average systolic	97.6		106.0		110.8			115.6					
					Average diastolic	64.8		70.8		72.9			78.6					
Aborigines of Australia	Australia	Nye [8]	1937	103	Average systolic						128		136.3		131.4		137.5	
					Average diastolic						78.5		78.3		75.6		75.0	
Chinese students	Canton, China	Cadbury [9]	1923	526	Average systolic	101		101										
					Average diastolic	61		68										
Miao tribe	Kweichow, China	Kilborn [10]	1937	150	Average systolic	108	106	109	106	103	100	99				100		
					Average diastolic	70	68	76	70	72	71	78				68		
Aboriginal Chinese tribes	Szechwan Province, West China	Morse and Beh [11]	1937	a. 143	Average systolic	103.5	111.9	108.1	106.2	107.3	107.9	107.1	119.5	113.0	106.5	116.0		
					Average diastolic	69.7	71.4	69.7	71.9	71.1	72.1	74.7	77.5	73.8	70.0	72.0		
a. Chwan Miao				b. 150	Average systolic	108	106	109	106	103	100	99			100			
b. Ta Hwa Miao					Average diastolic	70	68	76	70	72	71	68			73			
c. Noso				c. 105	Average systolic	98.6	104.7	107.7	102.7	101.8	106.3	106.2		99.6				
					Average diastolic	66.1	73.2	73.3	73.4	71.6	77.3	73.2		73.8				
Chinese	North China	Tung [12]	1930	1,233	Average systolic	102	104	104	106	107	109	113	113					% above 140 systolic, all ages—1.21
					Average diastolic	64	65	68	69	70	72	73	73					% above 90 diastolic, all ages—0.97
Chinese	China	Ling [13]	1936	15,114 men	Average systolic	114.4	113.6	113.9	115.0	117.2	119.6	121.9	124.6	127.2				Records of insurance applicants
					Average diastolic	72.4	74.0	74.1	75.0	77.3	78.8	79.9	81.0	82.3				
Chinese	Eastern Canada	Krakower [14]	1934	228	Average systolic			121.4		123.9		124.0		138.6		137.7		
					Average diastolic			82.7		82.3		82.0		88.2		87.8		
					% systolic 140 plus			3.2%		10.0%		9.8%		31.4%		33.3%		
					% diastolic 90 plus			16.1%		34.0%		26.1%		38.8%		41.6%		
					% systolic 150 plus			0%		6.9%		6.3%		20.3%		25.0%		
					% diastolic 100 plus			3.2%		10.0%		6.3%		11.1%		16.6%		

Healthy Chinese	Formosa	Rai [15]	1936	2,974	Average systolic	112.4	114.1	115.2	115.7	117.0	118.3	120.1	122.9	126.8	138.0	116.8		
					Average diastolic	66.1	69.0	71.9	73.1	74.0	75.9	77.0	77.2	79.2	80.0	73.7		
					I. Men. Poor Outpatients													
Japanese	Japan	Hashimoto, Akatsuka, Tsujii and Shiraishi [15a]	1933	16,393	% Hypertension		2.8	3.6	2.8	11.7	14.0	18.9	26.6	32.7	38.2	38.2	45.2	"Hypertension is defined as a persistent systolic pressure of 160 mm. of mercury or more or a persistent diastolic of 100 mm. of mercury or more"
					II. Women. Poor Outpatients													
					% Hypertension		3.7	6.1	8.9	12.3	16.0	16.7	29.2	34.6	45.8	44.1	71.8	
					III. Men. Pay Outpatients													
					% Hypertension		1.9	2.3	3.3	2.8	5.3	12.4	25.3	17.1	37.7	30.6	28.6	
					IV. Women. Pay Outpatients													
					% Hypertension		1.4	1.5	3.2	7.1	8.6	16.7	19.5	24.3	35.3	33.3	50.0	
Japanese	**Japan**	**Ishioka [15b]**	1921	.....	Average systolic	112.7	121.0	120.7	122.4	123.5	126.1	127.3	133.9					Data collected on accepted insurance risks
					Average diastolic	67.9	72.3	73.5	74.5	76.0	76.5	77.1	80.9					
Hindus, Moslems, Sikhs, Christians, Persians and Afghans	India	Chopra, R. N.; Chopra, G. S., and Chopra, I. C.[16]	1942	10,000	Average systolic	109.2	111.5	112.0	113.6	118.6	120.4	122.8	126.2	126.4	128.0	128.6	130.2	
					Average diastolic	70	72.4	71.2	72.0	72.6	73.2	75.0	77.1	80.4	82.5	82.8	83.0	
Indian Teagarden Laborers	Upper Assam, India	Dey [17]	1942	200	Average systolic	115	117	115	120	122	125	125	127	127	135			
					Average diastolic	72	75	75	75	75	80	80	80	80	85			
Filipinos	Philippine Islands	Concepcion and Bulatao [18]	1916	a. 536 men	Average systolic	110.7		111.9		118.8		125.4		129.0		137.8		
					Average diastolic	77.6		76.6		80.3		86.6		86.2		91.6		
				b. 181 women	Average systolic	109.2		118.1		118.2				132.9 (41-60 yr.)				
					Average diastolic	80.8		84.1		85.2				90.5 (41-60 yr.)				
Mixed Group Filipinos	Philippine Islands	Musgrave and Sison [19]	1910	140	Average systolic	117	104	125	122	115	130	135						
	Philippine Islands	Saleedo and Pascual [20]	1932	2,000														Data rearranged to conform to our scheme
				a. men	Average systolic			115.2		118.9		123.9		128.3		128.4		
					Average diastolic			67.9		74.1		76.9		80.6		84.9		
				b. women	Average systolic			109.4		114.3		127.2		130.8		140.0		
					Average diastolic			70.0		73.3		78.3		81.8		78.5		
Puerto Ricans	Puerto Rico	Ashford [21]	1930	126														
				a. men.	Average systolic	104		110.7		114.7		115.6		123.8				
					Average diastolic	60		65		70.9		70.4		75.9				
				b. women	Average systolic	111.2		109.5		114.1		123.9		125.6				
					Average diastolic	68.7		69.1		72.3		76.2		92.0				
	Puerto Rico	Rodriquez Molina and Suarez [22]	1930	176														
				a. men	Average systolic		111.1	121.3	119.8	118.7	122.7	125.0	123.5					Average blood pressure, all ages—123.6/76.1
					Average diastolic		63.8	74.6	75.1	77.8	77.2	75.2	78.5					
				b. women	Average systolic		113.2	113.5	117.9	117.0	129.0	119.3						
					Average diastolic		74.2	74.0	71.0	74.0	80.0	81.0						

Blood Pressures of Various Races—Concluded

Race	Country	Observers	Year	Number of Cases		Age, Years 15-20	20-25	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70	Over 70	Comment
West Indians and Panamanians	Isthmus of Panama	Kean [6]	1941	787 Panamanians	Average systolic	104.9		106.6		102.9		115.0						In a second study of 3,202 men a systolic blood pressure of 150 plus was found among 6.4% of Panamanians and 23.5% of West Indians In a third study of 1,711 pregnant women, a systolic blood pressure of 150 plus was found among 2.9% of Panamanians and 10.7% of West Indians
					Average diastolic	72.2		73.9		76.3		76.9						
					% systolic 150 plus	0.3		0.7		3.1		9.3						
					% diastolic 100 plus	0.5		2.2		3.1		5.6						
				541 West Indians	Average systolic	114.5		119.8		127.2		135.8						
					Average diastolic	78.1		83.0		88.8		91.6						
					% systolic 150 plus	4.2		7.1		20.4		33.9						
					% diastolic 100 plus	2.6		10.6		25.9		30.6						
Mayan (Yucatecan) and mixed Spanish and Indian	Mexico (Yucatan)	Saunders [23]	1933	1,066	Average systolic	112.0		112.4		119.4		122.5		130.7		132.6		132.2	Per cent having a systolic blood pressure of 150 plus was: Mayan men.....3.5% Mayan women.....8.0% Mestizo .....2.8% Mestiza 7.3%
					Average diastolic	70.2		71.7		75.6		75.0		75.3		73.3		74.2	
Guatemalans and Yucatecan Indians	Mexico and Guatemala	Shattuck [24]	1937	457 Total of Guatemalans and Indians	Average systolic	108.0		112.5		113.6		119.8				119.0		121.6	
					Average diastolic	71.6		71.6		68.4		70.7				82.9		78.7	
				344 Indians	Average diastolic	75.5		74.7		79.5		81.7				80.7		81.7	
Negro and White	Virgin Islands	Saunders and Bancroft [25]	1942	A. 1,849 Negro men	Average systolic		124.1				139.2					156.5			High incidence of hypertension
					Average diastolic		76.4				86.0					93.3			
				B. 2,523 Negro women	Average systolic		124.8				144.5					175.6			
					Average diastolic		77.3				88.9					98.0			
				C. 290 White men	Average systolic		120.9				131.8					152.1			
					Average diastolic		73.5				83.0					91.5			
				D. White women	Average systolic		122				128.4					156.4			
					Average diastolic		74.6				79.4					90.5			
Cuna Indians	San Blas Archipelago, Panama	Kean [26]	1944	407	Average systolic		107.9		104.4		103.7		104.5		105.3		109.4		Not a single hypertensive person found
					Average diastolic		70.9		69		69.4		70.0		66.0		66.7		
South American	Brazil	Albagli [27]	1942	618	Average systolic	127.5		123		124.5		128.0		128.1		135.0			
					Average diastolic	75		75.3		78.0		78.0		77.9		82.8			
South American	Uruguay	Rocha and de Giordano [28]	1943	4,943	Average systolic	120	127.5	127.5	130	130	130	130	132.5	142.5	142.5		142.5		
					Average diastolic	65	67.5	70	75	75	75	75	75	85	82.5		65		

1. Is the rise of blood pressure with age physiologic or pathologic?
2. Is civilization or the so-called civilizing influence responsible for an increase of arterial tension?

A survey of the literature was undertaken, and the results are summarized in the accompanying table. The paucity of studies among primitive people is immediately apparent. Undoubtedly valuable data have escaped our attention because they were either published in local journals or were included in general articles which were not indexed under helpful headings. Many studies were rejected because conclusions were based on inadequate data or because the method of making the blood pressure determinations was considered unreliable. Others were regretfully deleted from the table because they did not fit the arbitrary pattern of our study. None of the remaining papers presents unassailable evidence, and few are susceptible to rigid statistical evaluation. The reader will be quick to appreciate that while the obtaining of 5,000 blood pressure readings in the United States may simply require time and effort, 50 recordings in the African bush country may well represent the fruits of an expedition.

Most of the determinations recorded in the table were made by observers who used checked sphygmomanometers. The systolic blood pressure was recorded at the beginning of the first phase and the diastolic at the fourth phase.

The word "race" is used to mean simply a group of persons similar in appearance, cultural background and language. Few of the peoples studied represent true races.

COMMENT

If allowance is made for the relatively few persons examined, it seems that in Africa blood pressure does not rise with age. This is shown by the figures of Donnison,[5] that were confirmed by Williams.[6]

The studies on the Australian aborigines are thoroughly inadequate, and we can draw no conclusions from them.

Among the Chinese, three groups are easily recognizable. The poor Chinese, as can be seen in the studies of Kilborn,[10] Cadbury[9] and Morse and Beh,[11] have low arterial tension and no increase with age. In the wealthier groups, such as those analyzed by Ling,[13] there is a higher average blood pressure in each age group and a moderate increase with age. Among Chinese living in Canada[14] the figures are comparable to those of Symonds.[1]

The Japanese living in urban communities have average blood pressures which are comparable to those reported by Symonds, and the incidence of hypertension is apparently reasonably high. Data obtained on those living in rural areas would be of great interest.

In India and the Philippines the data are similar to those in the United States.

In the Caribbean area, West Indian Negroes, as shown by Kean,[29] Saunders and Bancroft,[25] Marvin and Smith[30] and Scrimshaw,[31] have a high incidence of hypertension and a distinct rise of arterial tension with increasing years. Panamanians have little hypertension and virtually no increase of blood pressure with age. (The failure to demonstrate hypertension among the Cuna Indians in Panama recalls the work of Fleming,[32] who observed much lower blood pressure averages in Zuni Indians than in white persons. He was unable to find any blood pressure above 145 mm. systolic or 85 mm. diastolic. Sixty-five of his group of 150 Indians were between 50 and 70 years of age.)

In Panama an effort has been made to study the reasons for the blood pressure differences between these two races. Marvin and Smith[30] revealed that the West Indian does not tolerate his high arterial tension in a benign fashion and that the incidence of cardiovascular-renal disease in West Indian Negroes living in Panama is many times greater than that in the Panamanians. Taylor[33] showed from autopsy material that there is much more renal disease, especially pyelonephritis, in West Indians than in Panamanians. At the present time Scrimshaw[34] is studying differences in diet between these two peoples.

CONCLUSIONS

1. In some races arterial tension does not rise with age. Doubt is cast, therefore, on the theory that there is a physiologic rise of arterial tension from adolescence to old age.

2. Among some peoples normal blood pressure is so low that they would be considered hypotensive by most physicians.

3. Economic status, climate and superficial psychologic strain do not appear to be significant factors in the genesis of hypertension.

4. Studies must be made of the disease, diet and deeply rooted psychologic problems of peoples to determine if any of these are important in producing hypertension.

5. A reevaluation of the enormous body of statistics must be made in the United States to determine whether the so-called normal increase of arterial tension is not due to the inclusion of cases of incipient and mild hypertension in the middle age and older age groups.

6. The gathering of more extensive and accurate data about the blood pressures of various races should be stimulated, and a repository of such information should be established, possibly by one of the heart associations.

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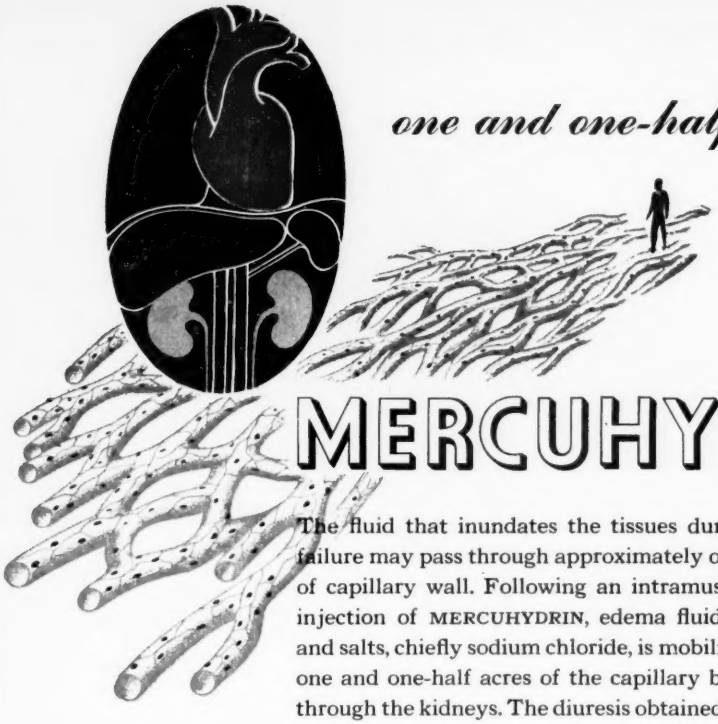

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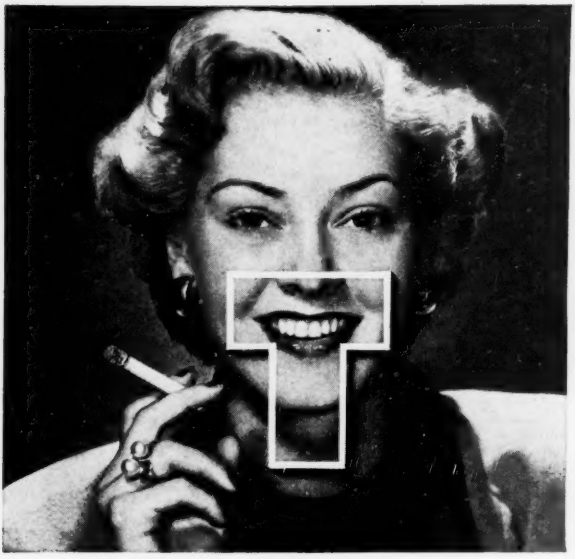

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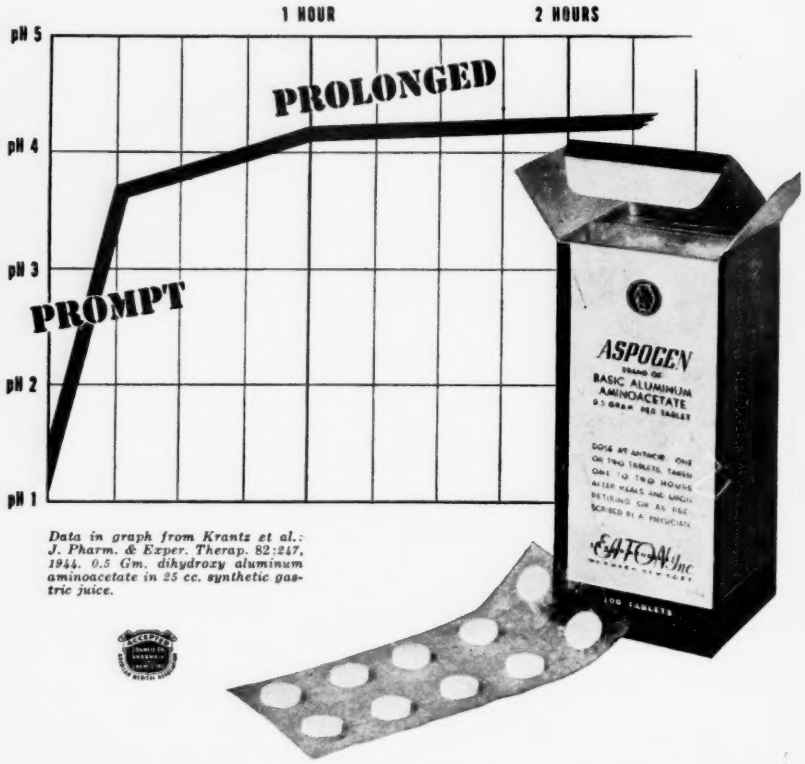

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